The American Association for the Study of Liver Diseases and the Infectious Diseases Society of America Present

HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C

Last Updated: September 21, 2017
www.hcvguidelines.org

AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES

IDSA
Infectious Diseases Society of America

Introduction

NOTICE: Guidance for hepatitis C treatment in adults is changing constantly with the advent of new therapies and other developments. A static version of this guidance, such as printouts of this website material, booklets, slides, and other materials, may be outdated by the time you read this. We urge you to review this guidance on this website (www.hcvguidelines.org) for the latest recommendations.

The landscape of treatment for hepatitis C virus (HCV) infection has evolved substantially since the introduction of highly effective HCV protease inhibitor therapies in 2011. The pace of change has increased rapidly as numerous new drugs with different mechanisms of action have become available over the past few years. To provide healthcare professionals with timely guidance as new therapies become available and are integrated into HCV regimens, the Infectious Diseases Society of America (IDSA) and American Association for the Study of Liver Diseases (AASLD), developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management.

The AASLD/IDSA guidance on hepatitis C addresses management issues ranging from testing and linkage to care, the crucial first steps toward improving health outcomes for HCV-infected persons, to the optimal treatment regimen in particular patient situations. Recommendations are evidence based and rapidly updated as new data from peer-reviewed research become available. For each treatment option, recommendations reflect the best possible management for a given patient and a given point of disease progression. Recommendations are rated with regard to the level of the evidence and strength of the recommendation. The AASLD/IDSA guidance on hepatitis C is supported by the membership-based societies and not by pharmaceutical companies or other commercial interests. The governing boards of AASLD and IDSA have appointed an oversight committee of 4 co-chairs and selected panel members from the societies.

This guidance should be considered a living document in that the recommendations are updated frequently as new information and treatments become available. This continually evolving report provides guidance on FDA-approved regimens. At times, it may also recommend off-label use of certain drugs or tests, or provide guidance for regimens not yet approved by the FDA. Readers should consult prescribing information and other resources for further information. In the future, treatment recommendations may be further guided by data from cost-effectiveness studies.

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Table 1. Summary of the Process and Methods for the Guidance Development

Topic	Description
Statement of need	Increased awareness of the rising number of complications of hepatitis C virus (HCV) infection, the recent screening initiatives by the Centers for Disease Control and Prevention (CDC) and US Preventive Services Task Force (USPSTF), and the rapid evolution of highly effective antiviral therapy for HCV infection have driven a need for timely guidance on how new developments change practice for healthcare professionals.
Goal of the guidance	The goal of the guidance is to provide up-to-date recommendations to healthcare practitioners on the optimal screening, management, and treatment for persons with HCV infection in the United States, considering the best available evidence. The guidance is updated regularly as new data, information, and tools and treatments become available.
Panel members	Panel members are chosen based on their expertise in the diagnosis, management, and treatment of HCV infection. Members from the fields of hepatology and infectious diseases are included, as well as HCV community representatives. Members are appointed by the sponsor societies after vetting by an appointed sponsor society committee. The panel chairs are appointed by the society boards, 2 each from the sponsor societies. All panel chairs and members serve as uncompensated volunteers for defined terms (2 to 3 years), which may be renewed based on panel needs.
Conflict of interest management	The panel was established with the goal of having no personal (ie, direct payment to the individual) financial conflicts of interest among its chairs and among fewer than half of its panel members. All potential panel members are asked to disclose any personal relationship(s) with pharmaceutical, biotechnology, medical device, or health-related companies or ventures that may result in financial benefit. Disclosures are obtained prior to the panel member appointments and for 1 year prior to the initiation of their work on the panel. Full transparency of potential financial conflicts is an important goal for the guidance that best ensures the credibility of the process and the recommendations. Individuals are also asked to disclose funding of HCV-related research activities to their institutional division, department, or practice group. Disclosures are reviewed by the HCV guidance chairs, who make assessments based on the conflict-of-interest policies of the sponsoring organizations (AASLD and IDSA). Personal and institutional financial relationships with commercial entities that have products in the field of hepatitis C are assessed. The following relationships are prohibited during membership on the guidance panel and are grounds for exclusion from the panel: • Employment with any commercial company with products in the field of hepatitis C • An ownership interest in a commercial entity that produces hepatitis C products • Participation in/payment for promotional or marketing activities sponsored by companies

Methods

The guidance was developed by a panel of HCV experts in the fields of hepatology and infectious diseases using an evidence-based review of information that is largely available to healthcare practitioners. The processes and detailed methods for developing the guidance are detailed in Methods Table 1. Recommendations are rated according to the strength of the recommendation and quality of the supporting evidence (see Methods Table 2) (AASLD-IDSA, 2015). Commonly used abbreviations are defined in Methods Table 3.

The panel regularly reviews available data to determine whether a regimen should be classified as recommended, alternative, or not recommended for particular patient subgroups. Recommended regimens are those that are favored for most patients in a given subgroup based on optimal efficacy, favorable tolerability and toxicity profiles, treatment duration, and pill burden. Alternative regimens are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. In certain circumstances, an alternative regimen may be optimal for a specific patient situation. Not recommended regimens are clearly inferior to recommended or alternative regimens due to factors such as lower efficacy, unfavorable tolerability and toxicity, longer treatment duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection.

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Topic	Description
	with HCV-related products including non-CME educational activities or speakers bureaus for audiences outside of the company • Participation in any single-funder CME activity • Participation on a marketing or medical affairs advisory board The following relationships or activities are reportable but do not merit exclusion: • Commercial support of research that is paid to an organization or practice group Due to the rapidly evolving nature of the subject matter, having individuals with expertise in the particular clinical topic is crucial to developing the highest-quality and most-informed recommendations. To that end, research support from commercial entities is not considered grounds for panel exclusion (an unresolvable conflict) if the funding of the research was paid to the institution or practice group, as opposed to the individual. In the instance of someone conducting clinical research in a community practice, research funds to the group practice are acceptable. • Participation on commercial company scientific advisory boards Participation in advisory boards, data safety monitoring boards, or in consultancies sponsored by the research arm of a company (eg, study design or data safety monitoring board) is considered a potential personal conflict that should be reported but is not considered a criterion for exclusion. • CME honorarium earned in excess of $5000 (total per year, including travel costs) No need to report if total honorarium is less than $5000. The HCV guidance chairs achieved a majority of panel members with no personal financial interests. Panel members are asked to inform the group of any changes to their disclosure status and are given the opportunity to recuse themselves (or be recused) from the discussion where a perceived conflict of interest that cannot be resolved exists. Financial disclosures for each panel member can be accessed here.
Intended audience	Medical practitioners, especially those who provide care to or manage patients with hepatitis C, are the intended audience of the guidance.
Sponsors, funding, and collaborating partner	AASLD and IDSA are the sponsors of the guidance and provide ongoing financial support. Grant support was sought and obtained from CDC for the initial gathering and review of evidence related to hepatitis C screening and testing recommendations and interventions to implement HCV screening in clinical settings.
Evidence identification and collection	The guidance is developed using an evidence-based review of information that is largely available to healthcare practitioners. Data from the following sources are considered by panel members when making recommendations: research published in the peer-reviewed literature or presented at major national or international scientific conferences; safety warnings from the US Food and Drug Administration (FDA) or other regulatory agencies or from manufacturers; drug interaction data; prescribing information from FDA-approved products; and registration data for

AASLD IDSA **Table 1. Summary of the Process and Methods for the Gui...**
From www.HCVGuidance.org on March 19, 2018

Topic	Description
	new products under FDA review. Press releases, unpublished reports, and personal communications are generally not considered. Literature searches are conducted regularly and before each major revision to ensure that the panel addresses all relevant published data. Medical subject headings and free text terms are combined to maximize retrieval of relevant citations from the PubMed, Scopus, EMBASE, and Web of Science databases. To be considered for inclusion, articles are required to have been published in English from 2010 to the present. Data from abstracts presented at national or international scientific conferences are also considered.
Rating of the evidence and recommendations	The guidance is presented in the form of recommendations. Each recommendation is rated in terms of the level of the evidence and strength of the recommendation using a modification of the scale adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (AHA, 2011); (Shiffman, 2003). A summary of the supporting (and conflicting) evidence follows each recommendation or set of recommendations.
Data review and synthesis and preparation of recommendations and supporting information	Draft recommendations are developed by subgroups of the full panel with interest and expertise in particular sections of the guidance. Following development of supporting text and references, the sections are reviewed by the full panel and chairs. A penultimate draft is submitted to the AASLD and IDSA governing boards for final review and approval before posting online on the website, www.hcvguidelines.org. Subgroups of the panel meet regularly by conference call as needed to update recommendations and supporting evidence. Updates may be prompted by new publications or presentations at major national or international scientific conferences, new drug approvals (or new indications, dosing formulations, or frequency of dosing), new safety warnings, or other information that may have a substantial impact on the clinical care of patients. Updates and changes to the guidance are indicated by a notice of update posted on the home page.
Abbreviations	Commonly used abbreviations in the text are defined in Methods Table 3.
Opportunity for comments	Evidence-based comments may be submitted to the panel by email to slynes@aasld.org or by clicking on the "Submit" button on the site contact form. The panel considers evidence-based comments about the recommendations, ratings, and evidence summaries but should not be contacted for individual patient management questions.

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Table 2. Rating System Used to Rate Level of Evidence and Strength of Recommendation

Recommendations are based on scientific evidence and expert opinion. Each recommended statement includes a Roman numeral (I, II, or III) representing the level of the evidence that supports the recommendation and a letter (A, B, or C) representing the strength of the recommendation.

Class	
I	Evidence and/or general agreement that a given diagnostic evaluation, procedure, or treatment is beneficial, useful, and effective.
II	Conflicting evidence and/or a divergence of opinion about the usefulness and efficacy of a diagnostic evaluation, procedure, or treatment.
IIa	Weight of evidence and/or opinion is in favor of usefulness and efficacy.
IIb	Usefulness and efficacy are less well established by evidence and/or opinion.
III	Conditions for which there is evidence and/or general agreement that a diagnostic evaluation, procedure, or treatment is not useful and effective or if it in some cases may be harmful.

Level	
A	Data derived from multiple randomized clinical trials, meta-analyses, or equivalent.
B	Data derived from a single randomized trial, nonrandomized studies, or equivalent.
C	Consensus opinion of experts, case studies, or standard of care.

Adapted from the American College of Cardiology and the American Heart Association Practice Guidelines (AHA, 2011); (Shiffman, 2003).

In some situations, such as for interferon-sparing HCV treatments, randomized clinical trials with an existing standard-of-care arm cannot ethically or practicably be conducted. The US Food and Drug Administration (FDA) has suggested alternative study designs, including historical controls or immediate versus deferred placebo-controlled trials. For additional examples and definitions see FDA link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM225333.pdf. In those instances for which there was a single predetermined, FDA-approved equivalency established, panel members considered the evidence as equivalent to a randomized controlled trial for levels A or B.

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Table 3. Commonly Used Abbreviations

Abbreviation	Definition and Notes
ACA	Patient Protection and Affordable Care Act
AFP	alpha-fetoprotein
ALT	alanine aminotransferase
AMP	average manufacturer price
Anti-HCV	HCV antibody
APRI	AST-to-platelet ratio index
AST	aspartate aminotransferase
AUC	area under the curve
AWP	average wholesale price[a]
BOC	boceprevir
CBC	complete blood count
CDC	Centers for Disease Control and Prevention
CEA	cost-effectiveness analysis
CTP	Child-Turcotte-Pugh (see below)
CYP	cytochrome P450
DAA	direct-acting antiviral
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
FDA	US Food and Drug Administration
GFR	glomerular filtration rate
HBsAg	hepatitis B virus surface antigen
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCV	hepatitis C virus Hepatitis C virus and HCV refer to the virus. Hepatitis C and HCV infection or HCV disease refer to the disease entity.

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Abbreviation	Definition and Notes
ICER	incremental cost-effectiveness ratio
IDU	injection drug use or user
INR	international normalized ratio
MELD	model for end-stage liver disease
MSM	men who have sex with men
NASH	nonalcoholic steatohepatitis
NAT	nucleic acid testing
NIH	National Institutes of Health
NS3	HCV nonstructural protein 3
NS5A	HCV nonstructural protein 5A
OATP	organic anion-transporting polypeptide
PBM	pharmacy benefit manager
PCR	polymerase chain reaction
P-gp	P-glycoprotein
PreP	preexposure prophylaxis
PWID	people who inject drugs
QALY	quality-adjusted life-year
RAS	resistance-associated substitution
RBC	red blood cell(s)
RBV	ribavirin
RGT	response-guided therapy
sAg	surface antigen
SMV	simeprevir
SOF	sofosbuvir
SVR12 (or 24 or 48, etc)	sustained virologic response at 12 weeks (or at 24 weeks, or at 48 weeks, etc)
TSH	thyroid-stimulating hormone
TVR	telaprevir

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Abbreviation	Definition and Notes
ULN	upper limit of normal
USPSTF	US Preventive Services Task Force
WAC	wholesale acquisition cost[b]

[a] "List price" for wholesale pharmacies to purchase drugs
[b] Typically, approximately 17% off of AWP

Child-Turcotte-Pugh (CTP) Classification of the Severity of Cirrhosis

	CLASS A	CLASS B	CLASS C
Total Points	5-6	7-9	10-15
Factor	1 Point	2 Points	3 Points
Total bilirubin (μmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
Prothrombin time / international normalized ratio	<1.7	1.71-2.3	>2.3
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or supressed with medication)	Grade III-IV (or refractory)

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Testing, Evaluation, and Monitoring of Hepatitis C

The following pages address testing, evaluation, and monitoring of patients with HCV before, during and after antiviral therapy.

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HCV Testing and Linkage to Care

One-Time Hepatitis C Testing

Recommendations for One-Time Hepatitis C Testing

RECOMMENDED	RATING
One-time hepatitis C testing is recommended for persons born[a] from 1945 through 1965 without prior ascertainment of risk.	I, B

Other persons should be screened for HCV infection risk factors. One-time testing should be performed for all persons with behaviors, exposures, and conditions or circumstances associated with an increased risk of HCV infection.
 	
Risk Behaviors
 	
• Injection-drug use (current or ever, including those who injected only once)
• Intranasal illicit drug use
 	
Risk Exposures
 	
• Persons on long-term hemodialysis (ever)
• Persons with percutaneous/parenteral exposures in an unregulated setting
• Healthcare, emergency medical, and public safety workers after needle-stick, sharps, or mucosal exposures to HCV-infected blood
• Children born to HCV-infected women
• Prior recipients of transfusions or organ transplants, including persons who:
  ◦ Were notified that they received blood from a donor who later tested positive for HCV
  ◦ Received a transfusion of blood or blood components, or underwent an organ transplant before July 1992
  ◦ Received clotting factor concentrates produced before 1987
• Persons who were ever incarcerated
 	
Other Conditions and Circumstances
 	
• HIV infection
• Sexually-active persons about to start pre-exposure prophylaxis (PrePP) for HIV
• Unexplained chronic liver disease and/or chronic hepatitis, including elevated alanine aminotransferase (ALT) levels
• Solid organ donors (deceased and living)
	I, B

[a] Regardless of country of birth

There are an estimated 3.5 million HCV-infected persons in the United States, including 2.7 million in the general noninstitutionalized population (Denniston, 2014) and 800,000 incarcerated, institutionalized, or homeless persons (Edlin, 2015). Approximately 50% of all infected people are unaware that they have HCV (Denniston, 2012); (Holmberg, 2013).

HCV testing is recommended in select populations based on demographics, possible exposures, high-risk behaviors, and medical conditions. Testing recommendations are based on HCV prevalence in these populations; proven benefits of care and treatment in reducing the risk of hepatocellular carcinoma and all-cause mortality; and the potential public health benefit of reducing transmission through early treatment, viral clearance, and reduced risk behaviors (Smith, 2012); (USPSTF, 2013); (CDC, 1998).

HCV is primarily transmitted through percutaneous exposure to infected blood. Other modes of transmission include mother-to-infant and contaminated devices shared for noninjection drug use. Sexual transmission also occurs but generally seems inefficient except among HIV-infected men who have unprotected sex with men (Schmidt, 2014).

Injection drug use poses the most significant risk for HCV infection, accounting for at least 60% of acute HCV infections in the United States. Healthcare exposures are important sources of transmission, including the receipt of blood products prior to 1992 (after which routine screening of the blood supply was implemented); receipt of clotting factor concentrates before 1987; long-term hemodialysis; needle-stick injuries among healthcare workers; and patient-to-patient transmission resulting from poor infection control practices.

Other risk factors include having been born to an HCV-infected mother, having been incarcerated, and percutaneous or parenteral exposures in an unregulated setting. Examples of these settings include tattoos received outside of licensed parlors and medical procedures done internationally or domestically where strict infection control procedures may not have been followed (eg, surgery before implementation of universal precautions) (Hellard, 2004).

The importance of these risk factors might differ based on geographic location and population (USPSTF, 2013); (CDC, 1998). An estimated 29% of incarcerated persons in North America are HCV-antibody–positive, supporting the recommendation to screen this population for HCV (Larney, 2013).

Because of shared transmission modes, persons with HIV infection are at risk for HCV. Sexual transmission is a particular risk for HIV-infected men who have unprotected sex with men (Hosein, 2013); (van de Laar, 2010). Screening sexually active, non-HIV-infected persons before they start pre-exposure prophylaxis (PreP) for HIV infection prevention should also be considered (Volk, 2015).

Recent data support testing in all deceased and living solid organ donors because of the risk of HCV infection posed to the recipient (Seem, 2013); (Lai, 2013). Although hepatitis C testing guidelines from the US Centers for Disease Control and Prevention (CDC) and the US Preventive Services Task Force (USPSTF) do not specifically recommend testing immigrants from countries with a high prevalence of HCV infection (eg, Egypt and Pakistan), such persons should be tested if they were born from 1945 through 1965, or if they have risk factors for infection (see One-Time Testing Recommendations).

CDC established risk-based HCV testing guidelines in 1998 (CDC, 1998). These guidelines were expanded in 2012 with a recommendation to offer a one-time HCV testing to all persons born from 1945 through 1965 without prior ascertainment of HCV risk factors (see One-Time Testing Recommendations). This recommendation was supported by evidence demonstrating that a risk-based strategy alone failed to identify more than 50% of HCV infections, due in part to patient underreporting of their risk and provider limitations in ascertaining risk factor information. Furthermore, persons in the 1945 through 1965 birth cohort account for nearly 75% of all HCV infections, with a 5-fold higher prevalence (3.25%) than other adults. This reflects a higher incidence of HCV infections in the 1970s and 1980s (peaking at 230,000 annually in the US, compared to an estimated 30,500 in 2014) (CDC, 2016). A retrospective analysis published in 2013 showed that 68% of persons with HCV infection would have been identified with a birth cohort testing strategy, whereas only 27% would have been screened with the risk-based approach (Mahajan, 2013). The cost-effectiveness of one-time birth cohort testing is comparable to that of current risk-based screening strategies (Smith, 2012).

Both CDC and the USPSTF recommend a one-time HCV test in asymptomatic persons belonging to the 1945 through 1965 birth cohort, as well as other individuals based on exposures, behaviors, and conditions or circumstances that

increase HCV infection risk.

HCV Testing for Persons With Ongoing Risk Factors

Recommendation for HCV Testing for Persons With Ongoing Risk Factors	
RECOMMENDED	RATING
Annual HCV testing is recommended for persons who inject drugs and for HIV-infected men who have unprotected sex with men. Periodic testing should be offered to other persons with ongoing risk factors for HCV exposure.	IIa, C

Evidence regarding the frequency of testing in persons at risk for ongoing exposures to HCV is lacking. Therefore, clinicians should determine the periodicity of testing based on the risk of infection or reinfection. Because of the high incidence of HCV infection among persons who inject drugs and HIV-infected men who have unprotected sex with men, HCV testing at least annually is recommended for these populations (Aberg, 2014); (Linas, 2012); (Wandeler, 2012); (Witt, 2013); (Bravo, 2012); (Williams, 2011).

Implementation of clinical decision support tools or prompts for HCV testing in electronic health records could facilitate reminding clinicians of HCV testing when indicated (Hsu, 2013); (Litwin, 2012); (http://nvhr.org/EMR).

Initial HCV Testing and Follow-Up

Recommendations for Initial HCV Testing and Follow-Up	
RECOMMENDED	RATING
An HCV-antibody test is recommended for initial HCV testing. If the result is positive, current infection should be confirmed by a sensitive HCV-RNA test.	I, A
Among persons with a negative HCV-antibody test who are suspected of having liver disease, testing for HCV RNA or follow-up testing for HCV antibody is recommended if exposure to HCV occurred within the past 6 months; testing for HCV RNA can also be considered for persons who are immunocompromised.	I, C
Among persons at risk of reinfection after previous spontaneous or treatment-related viral clearance, initial HCV-RNA testing is recommended because an HCV-antibody test is expected to be positive.	I, C
Quantitative HCV-RNA testing is recommended prior to initiation of antiviral therapy to document the baseline level of viremia (ie, baseline viral load).	I, A
HCV genotype testing is recommended to guide selection of the most appropriate antiviral regimen.	I, A
Persons found to have a positive HCV-antibody test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have evidence of current (active) HCV infection.	I, A

All persons recommended for HCV screening should initially be tested for HCV antibody (CDC, 2013); (Alter, 2003) using an assay approved by the US Food and Drug Administration (FDA). FDA-approved tests include laboratory-based assays and a point-of-care assay (ie, OraQuick HCV Rapid Antibody Test [OraSure Technologies]) (Lee, 2011). The latter is an indirect immunoassay with a sensitivity and specificity similar to those of laboratory-based HCV-antibody assays.

A positive test result for HCV antibody indicates either current (active) HCV infection (acute or chronic), past infection that has resolved, or a false-positive result (Pawlotsky, 2002). Therefore, an HCV nucleic acid test (NAT) to detect viremia is necessary to confirm active HCV infection and guide clinical management, including initiation of HCV treatment. HCV-RNA testing should also be performed in persons with a negative HCV-antibody test who are either immunocompromised (eg, persons receiving chronic hemodialysis) (KDIGO, 2008) or who might have been exposed to HCV within the last 6 months because these persons may be HCV-antibody–negative. An HCV-RNA test is also needed to detect reinfection in HCV-antibody–positive persons after previous spontaneous or treatment-related viral clearance.

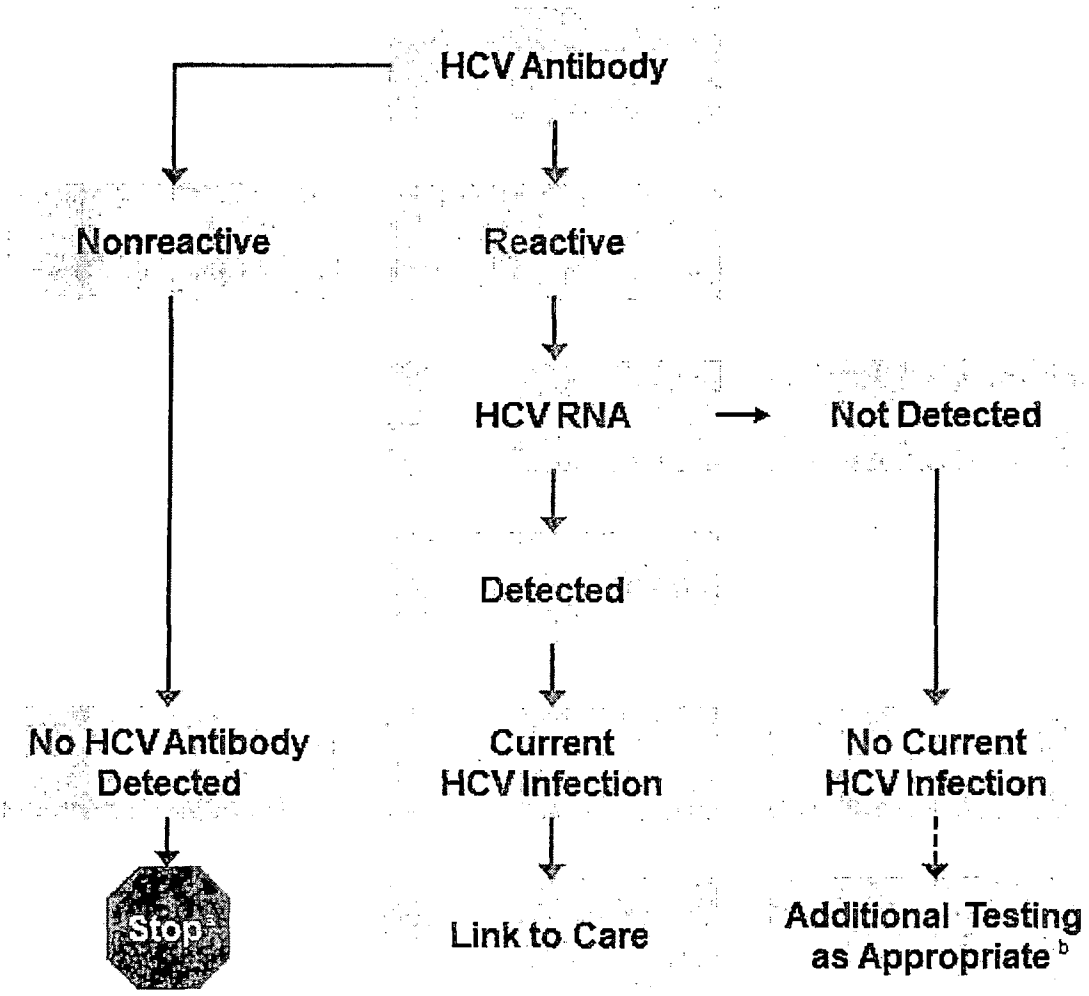
An FDA-approved quantitative or qualitative NAT with a detection level of 25 IU/mL or lower should be used to detect HCV RNA. Table 1 lists FDA-approved, commercially available HCV-antibody screening assays. Figure 1 shows the CDC-recommended testing algorithm.

Table 1. FDA-Approved HCV-Antibody Screening Assays

Assay	Manufacturer	Format
Abbott HCV EIA 2.0	Abbott Laboratories Abbott Park, IL, USA	EIA[a] (manual)
Advia Centaur HCV	Siemens Healthcare Malvern, PA, USA	CIA[b] (automated)
Architect Anti-HCV	Abbott Laboratories Abbott Park, IL, USA	CMIA[c] (automated)
AxSYM Anti-HCV	Abbott Laboratories Abbott Park, IL, USA	MEIA[d] (automated)
OraQuick HCV Rapid Antibody Test	OraSure Technologies, Inc. Bethlehem, PA, USA	Immunochromatographic (manual)
Ortho HCV Version 3.0 ELISA Test System	Ortho-Clinical Diagnostics, Inc. Raritan, NJ, USA	EIA[a] (manual)
VITROS Anti-HCV	Ortho-Clinical Diagnostics, Inc. Raritan, NJ, USA	CIA[b] (automated)

[a] EIA: enzyme immunoassay
[b] CIA: chemiluminescent immunoassay
[c] CMIA: chemiluminescent microparticle immunoassay
[d] MEIA: microparticle enzyme immunoassay
Table prepared by Saleem Kamili, PhD, Centers for Disease Control and Prevention.

Figure 1. CDC-Recommended Testing Sequence for Identifying Current HCV Infection



[a] For persons who might have been exposed to HCV within the past 6 months, testing for HCV RNA or follow-up testing for HCV antibody should be performed. For persons who are immunocompromised, testing for HCV RNA should be performed.
[b] To differentiate past, resolved HCV infection from biologic false positivity for HCV antibody, testing with another HCV-antibody assay can be considered. Repeat HCV-RNA testing if the person tested is suspected to have had HCV exposure within the past 6 months or has clinical evidence of HCV disease, or if there is concern regarding the handling or storage of the test specimen.
Adapted from Centers for Disease Control and Prevention (CDC), 2013 (CDC, 2013)

Persons who have a positive HCV-antibody test and negative results for HCV RNA by polymerase chain reaction (PCR) should be informed that they do not have laboratory evidence of current HCV infection. Additional HCV testing is typically unnecessary. The HCV-RNA test can be repeated when there is a high index of suspicion for recent infection or in patients with ongoing HCV infection risk.

Clinicians (or patients) may seek additional testing to determine whether a positive HCV-antibody test represents a remote HCV infection that has resolved or a false positive. For patients with no apparent risk for HCV infection, the likelihood of a false-positive HCV-antibody test is directly related to the HCV prevalence in the tested population. False-positive HCV-antibody tests most commonly occur in populations with a low prevalence of HCV infection (Alter, 2003). If further testing is desired to distinguish between a true positive vs biologic false positivity for HCV antibody, repeat testing may be done with a different FDA-approved, HCV-antibody assay. A biologic false result should not occur with two different assays (Vermeersch, 2008); (CDC, 2013).

Prior to initiation of antiviral therapy, quantitative HCV-RNA testing may be used to determine the baseline level of viremia (ie, viral load), which may affect treatment duration with certain regimens. The degree of viral load decline after initiation of treatment is less predictive of sustained virologic response (SVR) in the era of direct-acting antiviral (DAA) therapy compared to previous interferon-based treatment (see Pretreatment and On-Treatment Monitoring). Testing for HCV genotype helps guide selection of the most appropriate antiviral regimen.

Counseling Persons With Active HCV Infection

Recommendations for Counseling Persons With Active HCV Infection

RECOMMENDED	RATING
Persons with current HCV infection should receive education and interventions aimed at reducing liver disease progression and preventing HCV transmission.	IIa, B
Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.	IIa, B
Evaluation for other conditions that may accelerate liver fibrosis, including hepatitis B and HIV infections, is recommended for all persons with active HCV infection.	IIb, B
Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection to facilitate an appropriate decision regarding HCV treatment strategy, and to determine the need for initiating additional measures for cirrhosis management (eg, hepatocellular carcinoma screening) (see Monitoring section).	I, A
Vaccination against hepatitis A and hepatitis B is recommended for all susceptible persons with HCV infection.	IIa, C
Vaccination against pneumococcal infection is recommended for all patients with cirrhosis.	IIa, C
All persons with HCV infection should be provided education about how to avoid HCV transmission to others.	I, C

In addition to receiving antiviral therapy, HCV-infected persons should be educated about how to prevent further liver damage. Most important is prevention of the potential deleterious effect of alcohol. Numerous studies have found a strong association between excess alcohol use and the development or progression of liver fibrosis, and the development of hepatocellular carcinoma (Poynard, 1997); (Harris, 2001); (Wiley, 1998); (Corrao, 1998); (Bellentani, 1999); (Noda, 1996); (Safdar, 2004).

Daily consumption of more than 50 grams of alcohol has a high likelihood of worsening fibrosis. Some studies indicate that daily consumption of smaller amounts of alcohol also has a deleterious effect on the liver; however, these data are controversial (Westin, 2002); (Younossi, 2013b); (Hagström, 2017). Excess alcohol intake may also cause steatohepatitis. Alcohol screening and brief interventions, such as those outlined by the National Institute on Alcohol Abuse and Alcoholism, have been demonstrated to reduce alcohol consumption and episodes of binge drinking in the general population and among HCV-infected persons who consume alcohol heavily (Whitlock, 2004); (Dieperink, 2010); (Proeschold-Bell, 2012). Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist.

Hepatitis B virus (HBV) and HIV coinfection have been associated with a poorer HCV prognosis in cohort studies (Zarski, 1998); (Thein, 2008a); (Kruse, 2014); (Puoti, 2017b). Because of overlapping risk factors for these infections and benefits associated with their identification and treatment, HCV-infected persons should be tested for HIV antibody and hepatitis B surface antigen (HBsAg) using standard screening assays (Moyer, 2013); (CDC, 2008); (see USPSTF HIV screening recommendations and CDC hepatitis B screening recommendations). Patients should also be counseled about how to reduce their risk of acquiring these infections, including through HBV vaccination.

Patients with obesity and metabolic syndrome having underlying insulin resistance are at increased risk for nonalcoholic fatty liver disease, which is a risk factor for accelerated fibrosis progression in HCV-infected persons (Hourigan, 1999); (Ortiz, 2002). Therefore, HCV-infected persons who are overweight or obese (defined by a body mass index of 25 to 29.9 kg/m^2, and ≥30 kg/m^2, respectively) should be counseled regarding strategies to reduce body weight and improve insulin resistance via diet, exercise, and medical therapies (Musso, 2010); (Shaw, 2006). HCV-infected patients with hyperlipidemia or cardiovascular comorbidities may also benefit from lipid-lowering drugs. Prospective studies have demonstrated the safety and efficacy of statins in patients with chronic HCV and others with compensated chronic liver disease (Kamal, 2017); (Lewis, 2007). Therefore, these agents should not be withheld from HCV-infected patients.

The severity of liver disease associated with chronic HCV infection is a key factor in determining the initial and follow-up evaluation of patients. Although patients with more advanced disease may have a lower response to HCV therapy, they are also most likely to derive the greatest survival benefit (Ghany, 2011). A liver biopsy can provide objective, semiquantitative information regarding the amount and pattern of collagen or scar tissue in the liver, which can help inform the development of treatment and monitoring plans. The Metavir fibrosis score (F0 to F4) and Ishak fibrosis score (0 to 6) are commonly used to quantify the amount of hepatic collagen. A liver biopsy can also help assess the severity of liver inflammation and hepatic steatosis, and aid in excluding competing causes of liver injury (Kleiner, 2005). However, the procedure has a low but real risk of complications, and sampling artifact makes its serial use in most patients less desirable (Regev, 2002).

Noninvasive methods frequently used to estimate liver disease severity include:

- Liver-directed physical exam (normal in most patients)
- Routine blood tests (eg, ALT, AST, albumin, bilirubin, international normalized ratio [INR], and CBC with platelet count)
- Serum fibrosis marker panels
- Liver imaging (eg, ultrasound, or CT scan)
- Transient elastography

Simple calculations derived from routine blood tests—such as the serum AST-to-platelet ratio index (APRI) (Wai, 2003) and fibrosis-4 (FIB-4) (Sterling, 2006)—as well as assessment of liver surface nodularity and spleen size by liver ultrasound or other cross-sectional imaging modalities can help determine if patients with HCV have occult portal hypertension. The presence of portal hypertension is associated with a greater likelihood of developing future hepatic complications in untreated patients (Chou, 2013); (Rockey, 2006).

Liver elastography provides instant information regarding liver stiffness at the point of care and can reliably distinguish patients with a high versus low likelihood of cirrhosis (Castera, 2012); (Bonder, 2014). A more detailed discussion regarding fibrosis assessment is found in the When and In Whom to Initiate Therapy section.

Because persons with known or suspected bridging fibrosis and cirrhosis are at increased risk of developing complications of advanced liver disease, they require frequent follow-up. They should also avoid hepatotoxic drugs, such as excessive acetaminophen (>2 g/d) and certain herbal supplements. Nephrotoxic drugs, such as nonsteroidal anti-inflammatory drugs, should also be avoided. Ongoing imaging surveillance for liver cancer and gastroesophageal varices is also recommended for these patients (Sangiovanni, 2006); (Fontana, 2010). Persons with cirrhosis are more susceptible to invasive pneumococcal infection (Marrie, 2011) and should receive pneumococcal vaccination (CDC, 2012).

Exposure to infected blood is the primary mode of HCV transmission. HCV-infected persons must be informed of the precautions needed to avoid exposing others to infected blood. This is particularly important for persons who use injection drugs given that HCV transmission in this population primarily results from sharing needles and other contaminated drug injection equipment. Epidemics of acute HCV due to sexual transmission in HIV-infected men who have sex with men have also been described recently (van de Laar, 2009); (Urbanus, 2009); (Fierer, 2008). Table 2 outlines measures to avoid HCV transmission. HCV is not spread by sneezing, hugging, holding hands, coughing, or sharing eating utensils or drinking glasses, nor is it transmitted through food or water.

Table 2. Measures to Prevent HCV Transmission

HCV-infected persons should be counseled to avoid sharing toothbrushes and dental or shaving equipment, and be cautioned to cover any bleeding wound to prevent the possibility of others coming into contact with their blood.
Persons should be counseled to stop using illicit drugs and enter substance abuse treatment. Those who continue to inject drugs should be counseled to: • Avoid reusing or sharing syringes, needles, water, cotton, and other drug preparation equipment. • Use new sterile syringes and filters, and disinfected cookers. • Clean the injection site with a new alcohol swab. • Dispose of syringes and needles after 1 use in a safe, puncture-proof container.
Persons with HCV infection should be advised not to donate blood and to discuss HCV serostatus prior to donation of body organs, other tissue, or semen.
Persons with HIV infection and those with multiple sexual partners or sexually transmitted infections should be encouraged to use barrier precautions to prevent sexual transmission. Other persons with HCV infection should be counseled that the risk of sexual transmission is low and may not warrant barrier protection.
Household surfaces and implements contaminated with visible blood from an HCV-infected person should be cleaned using a dilution of 1 part household bleach to 9 parts water. Gloves should be worn when cleaning up blood spills.

Linkage to Care

Recommendation for Linkage to Care	
RECOMMENDED	RATING
All persons with active HCV infection should be linked to a clinician who is prepared to provide comprehensive management.	IIa, C

Improvement in identification of active HCV infection and advances in treatment regimens will have limited impact on HCV-related morbidity and mortality without concomitant improvement in linkage to care. All patients with current HCV infection and a positive HCV-RNA test result should be evaluated by a clinician with expertise in assessment of liver disease severity and HCV treatment. Subspecialty care and consultation are required for persons with HCV infection who have advanced fibrosis or cirrhosis (Metavir stage ≥F3), including possible referral for consideration of liver transplantation.

In the United States, only an estimated 13% to 18% of HCV-infected persons had received treatment by 2013 (Holmberg, 2013). Lack of appropriate clinician assessment and delays in linkage to care can result in negative health outcomes. Furthermore, patients who are lost to follow-up fail to benefit from evolving evaluation and treatment options.

Commonly cited patient-related barriers to treatment initiation include contraindications to treatment (eg, medical or psychiatric comorbidities); lack of acceptance of treatment (eg, asymptomatic nature of disease, competing priorities, low treatment efficacy, long treatment duration, and adverse effects); and lack of access to treatment (eg, cost and distance to specialist) (Khokhar, 2007); (Arora, 2011); (Clark, 2012).

Common clinician-related barriers include perceived patient-related barriers (eg, fear of adverse effects, treatment duration, cost, and effectiveness); lack of expertise in HCV treatment; lack of specialty referral resources; resistance to treating persons currently using illicit drugs or alcohol; and concern about the cost of HCV treatment (Morrill, 2005); (Reilley, 2013); (McGowan, 2013).

Data are lacking to support exclusion of HCV-infected persons from considerations for hepatitis C therapy based on the amount of alcohol intake or use of illicit drugs. Based on data from interferon-based treatment, SVR rates among people who inject drugs are comparable to those among people who do not inject drugs (Aspinall, 2013). Some possible strategies to address barriers to HCV treatment are listed in Table 3.

Table 3. Common Barriers to HCV Treatment and Potential Strategies

Barrier	Strategy
Contraindications to treatment (eg, comorbidities, substance abuse, and psychiatric disorders)	• Conduct counseling and education • Refer for services (eg, psychiatry and opioid substitution therapy) • Optimize treatment with simpler, less toxic regimens
Competing priorities and loss to follow-up	• Conduct counseling and education • Engage case managers and patient navigators (HIV model) • Co-localize services (eg, primary care, medical homes, and drug treatment)
Long treatment duration and adverse effects	• Optimize treatment with simpler, better tolerated regimens • Conduct appropriate education and monitoring • Utilize directly observed therapy (tuberculosis model)
Lack of access to treatment (eg, high cost, lack of insurance, geographic distance, and/or lack of availability of specialists)	• Leverage expansion of coverage through the Patient Protection and Affordable Care Act • Participate in models of care involving close collaboration between primary care clinicians and specialists • Liaise with pharmaceutical patient assistance programs • Co-localize services (primary care, medical homes, drug treatment)
Lack of practitioner expertise	• Collaborate with specialists (eg, Project ECHO-like models and telemedicine) • Develop accessible, clear HCV treatment guidelines • Develop electronic health record performance measures and clinical decision support tools (eg, pop-up reminders and standing orders)

One strategy that addresses several barriers is co-localization (integrated care) of HCV screening, evaluation, and treatment with other medical or social services. Co-localization has already been applied to settings with a high prevalence of HCV infection (eg, correctional facilities, needle exchange programs, substance abuse treatment centers, and methadone maintenance facilities) but this type of care is not uniformly available (Islam, 2012); (Stein, 2012); (Bruggmann, 2013). A study conducted by Ho and colleagues demonstrated that integrated care—consisting of multidisciplinary care coordination and patient case management—increased the proportion of patients with HCV infection and psychiatric illness or substance use who begin antiviral therapy and achieve a sustained virologic response, without serious adverse events (Ho, 2015).

A strategy that addresses lack of access to specialists—a primary barrier to hepatitis C care—is participation in models involving close collaboration between primary care practitioners and subspecialists (Arora, 2011); (Rossaro, 2013);

(Miller, 2012). Such collaborations have used telemedicine and knowledge networks to overcome geographic distances to specialists (Arora, 2011); (Rossaro, 2013). For example, Project ECHO (Extension for Community Healthcare Outcomes) uses videoconferencing to enhance primary care practitioner capacity in rendering HCV care and treatment to New Mexico's large rural and underserved population (Arora, 2011). Through case-based learning and real-time feedback from a multidisciplinary team of specialists (gastroenterology, infectious disease, pharmacology, and psychiatry practitioners), Project ECHO has expanded access to HCV treatment in populations that might have otherwise remained untreated. The short duration of treatment and few serious adverse events associated with DAA therapy present an opportunity to expand the number of midlevel practitioners and primary care physicians engaged in the management and treatment of HCV infection.

Additional strategies for enhancing linkage to and retention in care could be adapted from other fields, such as tuberculosis and HIV. For example, use of directly observed therapy has enhanced adherence to tuberculosis treatment, and use of case managers and patient navigators has reduced loss of follow-up in HIV care (Govindasamy, 2012). Recent hepatitis C testing and care programs have identified the use of patient navigators or care coordinators as important interventions in overcoming challenges associated with linkage to and retention in care (Trooskin, 2015); (Coyle, 2015). Ongoing assessment of efficacy and comparative effectiveness of this and additional strategies is a crucial area of future research for patients with HCV infection. Replication and expansion of best practices and new models for linkage to HCV care will also be crucial to maximize the public health impact of newer treatment paradigms.

Last update: September 21, 2017

When and in Whom to Initiate HCV Therapy

Successful hepatitis C treatment results in sustained virologic response (SVR), which is tantamount to virologic cure and, as such, is expected to benefit nearly all chronically infected persons. When the US Food and Drug Administration (FDA) approved the first interferon-sparing treatment for HCV infection, many patients who had previously been "warehoused" sought treatment. The infrastructure (ie, experienced practitioners, budgeted healthcare dollars, etc) did not yet exist to treat all patients immediately. Thus, the panel offered guidance for prioritizing treatment first for those with the greatest need.

Since that time, there have been opportunities to treat many of the highest-risk patients and accumulate real-world experience regarding the tolerability and safety of interferon-free HCV regimens. More importantly, from a medical standpoint, data continue to accumulate that demonstrate the many benefits, both intrahepatic and extrahepatic, that accompany HCV eradication. Therefore, the panel continues to recommend treatment for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy. Accordingly, prioritization tables have been removed from this section.

Despite the strong recommendation for treatment of nearly all HCV-infected patients, pretreatment assessment of a patient's understanding of treatment goals and provision of education about adherence and follow-up are essential. A well-established therapeutic relationship between clinician and patient remains crucial for optimal outcomes with direct-acting antiviral (DAA) therapies. Additionally, in certain settings there remain factors that impact access to medications and the ability to deliver them to patients. In these settings, clinicians may still need to decide which patients should be treated first. The descriptions of unique populations discussed in this section may help physicians make more informed treatment decisions for these groups. For additional information, see unique patient populations: Patients With HIV/HCV Coinfection, Patients With Decompensated Cirrhosis, Patients Who Develop Recurrent HCV Infection Post Liver Transplantation, Patients With Renal Impairment, HCV in Children, and HCV Post Kidney Transplant.

Goal of Treatment	
RECOMMENDED	RATING
The goal of treatment of HCV-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response.	I, A

Recommendation for When and in Whom to Initiate Treatment	
RECOMMENDED	RATING
Treatment is recommended for all patients with chronic HCV infection, except those with a short life expectancy that cannot be remediated by HCV therapy, liver transplantation, or another directed therapy. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert.	I, A

Clinical Benefit of Cure

The proximate goal of HCV therapy is SVR (virologic cure), defined as the continued absence of detectable HCV RNA for at least 12 weeks after completion of therapy. SVR is a marker for cure of HCV infection and has been shown to be durable in large prospective studies in more than 99% of patients followed-up for ≥5 years (Swain, 2010); (Manns, 2013). Patients in whom SVR is achieved have HCV antibodies but no longer have detectable HCV RNA in serum, liver tissue, or mononuclear cells, and achieve substantial improvement in liver histology (Marcellin, 1997); (Coppola, 2013); (Garcia-Bengoechea, 1999). Assessment of viral response, including documentation of SVR, requires use of an FDA-approved quantitative or qualitative nucleic acid test (NAT) with a detection level of ≤25 IU/mL.

Patients who are cured of their HCV infection experience numerous health benefits, including a decrease in liver inflammation as reflected by improved aminotransferase levels (ie, alanine aminotransferase [ALT] and aspartate aminotransferase [AST]), and a reduction in the rate of liver fibrosis progression (Poynard, 2002b). Among 3,010 treatment-naive patients from 4 randomized trials who had pretreatment and posttreatment liver biopsies (separated by a mean of 20 months) and were treated with 10 different interferon-based regimens, 39% to 73% of participants who achieved SVR had improvement in liver fibrosis and necrosis (Poynard, 2002b). Additionally, cirrhosis resolved in 49% of the cases. Portal hypertension, splenomegaly, and other clinical manifestations of advanced liver disease also improved. Among HCV-infected persons, SVR is associated with a >70% reduction in the risk of liver cancer (hepatocellular carcinoma [HCC]), and a 90% reduction in the risk of liver-related mortality and liver transplantation (Morgan, 2013); (van der Meer, 2012); (Veldt, 2007).

Cure of HCV infection also reduces symptoms and mortality from severe extrahepatic manifestations, including cryoglobulinemic vasculitis, a condition affecting 10% to 15% of HCV-infected patients (Fabrizi, 2013); (Landau, 2010); (Sise, 2016). HCV-infected persons with non-Hodgkin lymphoma and other lymphoproliferative disorders achieve complete or partial remission in up to 75% of cases following successful therapy for HCV infection (Gisbert, 2005); (Takahashi, 2012); (Svoboda, 2005); (Mazzaro, 2002); (Hermine, 2002). These reductions in disease severity contribute to dramatic reductions in all-cause mortality (van der Meer, 2012); (Backus, 2011). Furthermore, patients who achieve SVR have a substantially improved quality of life, which spans their physical, emotional, and social health (Boscarino, 2015); (Neary, 1999); (Younossi, 2013); (Gerber, 2016). Because of the many benefits associated with successful HCV treatment, clinicians should treat HCV-infected patients with antiviral therapy with the goal of achieving SVR, preferably early in the course of chronic HCV infection before the development of severe liver disease and other complications.

Benefits of Treatment at Early Fibrosis Stages (Metavir Stage Less Than F2)

Initiating therapy in patients with lower-stage fibrosis augments the benefits of SVR. In a long-term follow-up study, 820 patients with biopsy-confirmed Metavir stage F0 or F1 fibrosis were followed for up to 20 years (Jezequel, 2015). The 15-year survival rate was significantly better for those who experienced SVR than for those whose treatment failed or for those who remained untreated (93%, 82%, and 88%, respectively; P=.003). The study results argue for consideration of earlier initiation of treatment. Several modeling studies also suggest a greater mortality benefit if treatment is initiated at fibrosis stages prior to F3 (Øvrehus, 2015); (Zahnd, 2015); (McCombs, 2015).

Treatment delay may decrease the benefit of SVR. In a report from France, 820 patients with biopsy-confirmed Metavir stage F0 or F1 fibrosis were followed for as long as 20 years (Jezequel, 2015). The authors noted rapid progression of fibrosis in 15% of patients during follow-up, and in patients treated successfully, long-term survival was better. Specifically, at 15 years, survival rate was 92% for those with SVR versus 82% for treatment failures and 88% for those not treated. In a Danish regional registry study, investigators modeled treatment approaches with the aim of evaluating the benefit to the region in terms of reductions in morbidity and mortality and HCV prevalence (Øvrehus, 2015). Although they note that in their situation of low HCV prevalence (0.4%) with approximately 50% undiagnosed, a policy that restricts treatment to those with Metavir fibrosis stage F3 or higher would decrease mortality from HCC and cirrhosis, the number needed to treat to halve the prevalence of the disease is lower if all eligible patients receive treatment at diagnosis.

A modeling study based on the Swiss HIV cohort study also demonstrated that waiting to treat HCV infection until Metavir fibrosis stages F3 and F4 resulted in 2- and 5-times higher rates of liver-related mortality, respectively, compared with treating at Metavir stage F2 (Zahnd, 2015). A US Veterans Administration dataset analysis that used very limited end points of virologic response dating from the interferon-treatment era suggested that early initiation of therapy (at a fibrosis-4 [FIB-4] score of <3.25) increased the benefit attained with respect to likelihood of treatment success and mortality reduction, and ultimately decreased the number of patients needed to treat to preserve 1 life by almost 50% (McCombs, 2015).

Considerations in Specific Populations

Despite the recommendation for treatment of nearly all patients with HCV infection, it remains important for clinicians to understand patient- and disease-related factors that place individuals at risk for HCV-related complications (liver and extrahepatic) as well as for HCV transmission. Although these groups are no longer singled out for high prioritization for treatment, it is nonetheless important that clinicians recognize the unique dimensions of HCV disease and its natural history in these populations. The discussions offered below may assist clinicians in making compelling cases for insurance coverage of treatment when necessary.

Persons With Advanced Liver Disease

For persons with advanced liver disease (Metavir stage F3 or F4), the risk of developing complications of liver disease, such as hepatic decompensation (Child-Turcotte-Pugh [CTP] class B or C [Methods Table 3]) or HCC, is substantial and may occur in a relatively short timeframe. A large prospective study of patients with cirrhosis resulting from HCV infection examined the risk of decompensation—including HCC, ascites, jaundice, bleeding, and encephalopathy—and found that the overall annual incidence rate was 3.9% (Sanglovanni, 2006). The National Institutes of Health (NIH)-sponsored HALT-C study included a group of 220 patients with cirrhosis resulting from HCV infection who were observed for approximately 8 years. A primary outcome of death, hepatic decompensation, HCC, or an increase in CTP score ≥2 occurred at a rate of 7.5% per year (Everson, 2006); (Di Bisceglie, 2008). Patients with a CTP score of ≥7 experienced a death rate of 10% per year.

Numerous studies have demonstrated that hepatitis C therapy and the achievement of SVR in this population results in dramatic decreases in hepatic decompensation events, HCC, and liver-related mortality (Morgan, 2013); (van der Meer, 2012); (Backus, 2011); (Dienstag, 2011); (Berenguer, 2009); (Mira, 2013). In the HALT-C study, patients with advanced fibrosis secondary to HCV infection who achieved SVR, compared with patients with similarly advanced liver fibrosis who did not achieve SVR, had a decreased need for liver transplantation (HR, 0.17; 95% CI, 0.06-0.46), decreased development of liver-related morbidity and mortality (HR, 0.15; 95% CI, 0.06-0.38), and decreased HCC (HR, 0.19; 95% CI, 0.04-0.80) (Dienstag, 2011). Importantly, persons with advanced liver disease also require long-term follow-up and HCC surveillance regardless of treatment outcome (see Monitoring Patients Who Are Starting Hepatitis C Treatment, Are on Treatment, or Have Completed Therapy).

Given the clinical complexity and need for close monitoring, patients with advanced liver disease that has already decompensated (CTP class B or C [Methods Table 3]) should be treated by physicians with experience treating HCV in conjunction with a liver transplantation center, if possible (see Patients with Decompensated Cirrhosis).

Persons Who Have Undergone Liver Transplantation

In HCV-infected individuals, HCV infection of the liver allograft occurs universally in those with viremia at the time of transplantation. Histologic features of hepatitis develop in about 75% of recipients within the first 6 months following liver transplantation (Neumann, 2004). By the fifth postoperative year, up to 30% of untreated patients have progressed to cirrhosis (Neumann, 2004); (Charlton, 1998). A small proportion of patients (4% to 7%) develop an accelerated course of liver injury (cholestatic hepatitis C, associated with very high levels of viremia) with subsequent rapid allograft failure. Recurrence of HCV infection post transplantation is associated with decreased graft survival for recipients with HCV

infection compared to recipients who undergo liver transplantation for other indications (Forman, 2002).

Effective HCV therapy prior to transplantation resulting in SVR (virologic cure) prevents HCV recurrence post transplantation (Everson, 2003). In addition, complete HCV viral suppression prior to transplantation prevents recurrent HCV infection of the graft in the majority of cases (Forns, 2004); (Everson, 2005). Preliminary data from a study of patients with complications of cirrhosis secondary to HCV infection who were wait-listed for liver transplantation (included patients with MELD scores up to 14 and CTP scores up to 8) found that treatment with sofosbuvir and weight-based ribavirin for up to 48 weeks was well tolerated and associated with an overall posttransplant SVR rate of 70% (Curry, 2015). Posttransplant SVR was nearly universal among patients who had undetectable HCV RNA for 28 days or longer prior to transplantation.

Treatment of established HCV infection post transplantation also yields substantial improvements in patient and graft survival (Berenguer, 2008); (Picciotto, 2007). The availability of effective, interferon-free antiviral therapy has addressed the major hurdles to treating HCV recurrence post transplantation—poor tolerability and efficacy. A multicenter, open-label study evaluated the efficacy of sofosbuvir plus ribavirin to induce virologic suppression in 40 patients after liver transplantation with compensated recurrence of HCV infection. Daily sofosbuvir plus ribavirin for 24 weeks achieved SVR12 in 70% of these patients (Charlton, 2015). No deaths, graft losses, or episodes of rejection occurred. Six patients had serious adverse events, all of which were considered unrelated to the study treatment. There were no drug interactions reported between sofosbuvir and any of the concomitant immunosuppressive agents. In contrast, treatment with sofosbuvir plus ribavirin, with or without peginterferon, in 64 patients with severe, decompensated cirrhosis resulting from recurrence of HCV infection following liver transplantation was associated with an overall SVR12 rate of 59% and a mortality rate of 13% (Forns, 2015). On an intent-to-treat basis, treatment was associated with clinical improvement in 57% and stable disease in 22% of patients. Given the clinical complexity (including drug interactions and the need for close monitoring), patients with liver transplant should be treated by physicians with experience in treating this population (see Patients Who Develop Recurrent HCV Infection Post-Liver Transplantation).

Persons at Increased Risk for Rapidly Progressive Fibrosis and Cirrhosis

Fibrosis progression is variable across different patient populations as well as within the same individual over time. Many of the components that determine fibrosis progression and development of cirrhosis in an individual are unknown. However, certain factors, such as coinfection with HIV or the hepatitis B virus (HBV) and prevalent coexistent liver diseases (eg, nonalcoholic steatohepatitis [NASH]), are well-recognized contributors to accelerated fibrosis progression (see Table below).

HIV/HCV Coinfection

HIV coinfection accelerates fibrosis progression among HCV-infected persons (Benhamou, 1999); (Macias, 2009); (Konerman, 2014), although control of HIV replication and restoration of CD4 cell count may mitigate this to some extent (Benhamou, 2001); (Bräu, 2006). However, antiretroviral therapy is not a substitute for HCV treatment. In the largest paired-biopsy study, 282 HIV/HCV-coinfected patients with 435 paired biopsies were prospectively evaluated (Konerman, 2014). Thirty-four percent of patients showed fibrosis progression of at least 1 Metavir stage at a median of 2.5 years. Importantly, 45% of patients with no fibrosis on initial biopsy had progression. Finally, a more rapid progression to death following decompensation combined with lack of widespread access to liver transplantation and poor outcomes following transplantation highlight the need for HCV treatment in this population regardless of current fibrosis stage (see Patients with HIV/HCV Coinfection) (Pineda, 2005); (Merchante, 2006); (Terrault, 2012).

HBV/HCV Coinfection

The prevalence of HBV/HCV coinfection is estimated at 1.4% in the United States and 5% to 10% globally (Tyson, 2013); (Chu, 2008). Persons with HBV/HCV coinfection and detectable viremia of both viruses are at increased risk for disease progression, decompensated liver disease, and the development of HCC. HBV/HCV-coinfected individuals are susceptible to a process called viral interference wherein one virus may interfere with the replication of the other virus. Thus, when treating one or both viruses with antiviral drugs, periodic retesting of HBV DNA and HCV RNA levels during and after therapy is prudent, particularly if only one of the viruses is being treated at a time. Treatment of HCV infection in

such cases utilizes the same genotype-specific regimens as are recommended for HCV monoinfection (see Initial Treatment of HCV Infection). HBV infections in such cases should be treated as recommended for HBV monoinfection (Lok, 2009).

Other Coexistent Liver Diseases

Persons with other chronic liver diseases who have coincident chronic HCV infection should be considered for HCV therapy given the potential for rapid liver disease progression. An interferon-free regimen is generally preferred for immune-mediated liver diseases, such as autoimmune hepatitis, because of the potential for interferon-related exacerbation.

Persons With Extrahepatic Manifestations of Chronic HCV Infection

Cryoglobulinemia

Chronic hepatitis C is associated with a syndrome of cryoglobulinemia, an immune complex and lymphoproliferative disorder that leads to arthralgias, fatigue, palpable purpura, renal disease (eg, membranoproliferative glomerulonephritis), neurologic disease (eg, peripheral neuropathy, central nervous system vasculitis), and reduced complement levels (Agnello, 1992). Because patients with chronic hepatitis C frequently have laboratory evidence of cryoglobulins (>50% in some series), antiviral treatment is imperative for those with the syndrome of cryoglobulinemia and symptoms or objective evidence of end-organ manifestations. Interferon-based regimens can produce clinical remission; however, the adverse effects of interferon may mimic manifestations of cryoglobulinemia (Saadoun, 2014).

Glomerular disease results from deposition of HCV-related immune complexes in the glomeruli (Johnson, 1993). Successful treatment of HCV using interferon-based regimens can reverse proteinuria and nephrotic syndrome but usually does not fully ameliorate azotemia (Johnson, 1994). There is building new evidence of effective resolution of cryoglobulinemia upon clearance of HCV in most patients, making a strong case for HCV treatment in this clinical setting.

Diabetes

The relationship between chronic hepatitis C and diabetes (most notably type 2 diabetes and insulin resistance) is complex and incompletely understood. The prevalence and incidence of diabetes is increased in the context of hepatitis C (White, 2008). In the United States, type 2 diabetes occurs more frequently in HCV-infected patients, with a >3-fold greater risk in persons older than 40 years (Mehta, 2000). The positive correlation between quantity of plasma HCV RNA and established markers of insulin resistance confirms this relationship (Yoneda, 2007). Insulin resistance and type 2 diabetes are independent predictors of accelerated liver fibrosis progression (Petta, 2008). Patients with type 2 diabetes and insulin resistance are also at increased risk for HCC (Hung, 2010).

Successful antiviral treatment has been associated with improved markers of insulin resistance and a greatly reduced incidence of new-onset type 2 diabetes and insulin resistance in HCV-infected patients (Arase, 2009). Most recently, antiviral therapy for HCV infection has been shown to improve clinical outcomes related to diabetes. In a large prospective cohort from Taiwan, the incidence rates of end-stage renal disease, ischemic stroke, and acute coronary syndrome were greatly reduced in HCV-infected patients with diabetes who received antiviral therapy compared with untreated, matched controls (Hsu, 2014). Therefore, antiviral therapy may prevent progression to diabetes in HCV-infected patients with prediabetes, and may reduce renal and cardiovascular complications in HCV-infected patients with established diabetes.

Fatigue

Fatigue is the most frequently reported symptom in patients with chronic hepatitis C, and has a major effect on quality of life and activity level as evidenced by numerous measures of impaired quality of life (Foster, 1998). The presence and severity of fatigue appears to correlate poorly with disease activity, although it may be more common and severe in HCV-infected individuals with cirrhosis (Poynard, 2002a). Despite difficulties in separating fatigue symptoms associated with hepatitis C from those associated with other concurrent conditions (eg, anemia, depression), numerous studies have reported a reduction in fatigue after cure of HCV infection (Bonkovsky, 2007). In the Virahep-C study, 401 patients with HCV infection were evaluated for fatigue prior to and after treatment, using validated scales to assess the presence and

severity of fatigue (Sarkar, 2012). At baseline, 52% of patients reported having fatigue, which was more frequent and severe in patients with cirrhosis than in those without cirrhosis. Achieving SVR was associated with a substantial decrease in the frequency and severity of fatigue.

A recent analysis of 413 patients from the NEUTRINO and FUSION trials who were treated with a sofosbuvir-containing regimen and achieved SVR12 demonstrated improvement in patient fatigue (present in 12%) from the pretreatment level (Younossi, 2014). After achieving SVR12, participants had marked improvements in fatigue over their pretreatment scores, measured by 3 separate validated questionnaires. Additional studies support and extend these findings beyond fatigue, with improvements in overall health-related quality of life and work productivity observed following successful HCV therapy (Gerber, 2016); (Younossi, 2015b); (Younossi, 2015c); (Younossi, 2015d); (Younossi, 2015e); (Younossi, 2016a).

Dermatologic Manifestations

The reported prevalence of HCV infection in patients with porphyria cutanea tarda approximates 50% and occurs disproportionately in those with cirrhosis (Gisbert, 2003). The treatment of choice for active porphyria cutanea tarda is iron reduction by phlebotomy and maintenance of a mildly iron-reduced state without anemia. However, although improvement of porphyria cutanea tarda during HCV treatment with interferon has frequently been described (Takikawa, 1995), there are currently insufficient data to determine whether treating HCV infection with DAAs and achievement of SVR results in porphyria cutanea tarda improvement.

Lichen planus is characterized by pruritic papules involving mucous membranes, hair, and nails. HCV antibodies are present in 10% to 40% of patients with lichen planus but a causal link with chronic HCV infection is not established. Resolution of lichen planus has been reported with interferon-based regimens, but there have also been reports of exacerbation with these treatments. Although it is unknown whether DAAs will have more success against lichen planus, treatment with interferon-free regimens would appear to be a more advisable approach to addressing this disorder (Gumber, 1995); (Sayiner, 2017).

Benefit of Treatment to Reduce Transmission

Persons who have successfully achieved SVR (virologic cure) no longer transmit the virus to others. As such, successful treatment of HCV infection benefits public health. Several health models have shown that even modest increases in successful treatment of HCV infection among persons who inject drugs can decrease prevalence and incidence (Martin, 2013a); (Durier, 2012); (Martin, 2013b); (Hellard, 2012); (Harris, 2016). Models developed to estimate the impact of HCV testing and treatment on the burden of hepatitis C at a country level reveal that large decreases in HCV prevalence and incidence are possible as more persons are successfully treated (Wedemeyer, 2014).

There are also benefits to eradicating HCV infection between couples and among families, thus eliminating the perception that an individual might be contagious. In addition, mother-to-child transmission of HCV does not occur if the woman is not viremic, providing an additional benefit of curing a woman before she becomes pregnant (Thomas, 1998). However, the safety and efficacy of treating women who are already pregnant to prevent transmission to the fetus have not yet been established; thus, treatment is not recommended for pregnant women.

The Society for Healthcare Epidemiology of America (SHEA) advises that healthcare workers who have substantial HCV viral replication ($\geq 10^4$ genome equivalents/mL) be restricted from performing procedures that are prone to exposure (Henderson, 2010) and that all healthcare workers with confirmed chronic HCV infection should be treated. For reasons already stated, the achievement of SVR in such individuals will not only eliminate the risk of HCV transmission to patients but also decrease circumstantial loss of experienced clinicians. Given concerns about underreporting of infection and transmission (Henderson, 2010), the availability of effective, all-oral regimens should lead to greater willingness on the part of exposure-prone clinicians to be tested and treated.

Successful treatment of HCV-infected persons at greatest risk for transmission represents a formidable tool to help stop HCV transmission in those who continue to engage in high-risk behaviors. To guide implementation of hepatitis C treatment as a prevention strategy, studies are needed to define the best candidates for treatment to stop transmission, the additional interventions needed to maximize the benefits of HCV treatment (eg, preventing reinfection), and the cost-

effectiveness of the strategies when used in target populations.

Persons Who Inject Drugs

Injection drug use (IDU) is the most common risk factor for HCV infection in the United States and Europe, with an HCV seroprevalence rate of 10% to 70% (Amon, 2008); (Nelson, 2011). IDU also accounts for the majority of new HCV infections (approximately 70%) and is the key driving force in the perpetuation of the epidemic. Given these facts and the absence of an effective vaccine against HCV, testing and linkage to care combined with treatment of HCV infection with potent interferon-free regimens has the potential to dramatically decrease HCV incidence and prevalence (Martin, 2013b). However, treatment-based strategies to prevent HCV transmission have yet to be studied, including how to integrate hepatitis C treatment with other risk-reduction strategies (eg, opiate substitution therapy, and needle and syringe exchange programs) (Martin, 2013a).

In studies of interferon-based treatments in persons who inject drugs, adherence and efficacy rates are comparable to those of patients who do not use injected drugs. A meta-analysis of treatment with peginterferon, with or without ribavirin, in active or recent injection drug users showed SVR rates of 37% and 67% for genotype 1 or 4 and 2 or 3, respectively (Aspinall, 2013). With the introduction of shorter, better-tolerated, and more efficacious interferon-free therapies, these SVR rates are expected to improve. Importantly, the rate of reinfection in this population is lower (2.4/100 person-years of observation) than that of incident infection in the general population of injection drug users (6.1 to 27.2/100 person-years), although reinfection increases with active or ongoing IDU (6.44/100 person-years) and available data on follow-up duration are limited (Aspinall, 2013); (Grady, 2013).

Ideally, treatment of HCV-infected persons who inject drugs should be delivered in a multidisciplinary care setting with services to reduce the risk of reinfection and for management of the common social and psychiatric comorbidities in this population (Murphy 2015); (Dore, 2016); (Mathei 2016); (Midgard 2016). Regardless of the treatment setting, recent or active IDU should not be seen as an absolute contraindication to HCV therapy. There is strong evidence from various settings in which persons who inject drugs have demonstrated adherence to treatment and low rates of reinfection, countering arguments that have been commonly used to limit treatment access in this patient population (Aspinall, 2013); (Hellard, 2014); (Grebely, 2011). Indeed, combining HCV treatment with needle exchange and opioid agonist therapy programs in this population with a high prevalence of HCV infection has shown great value in decreasing the burden of HCV disease. Elegant modeling studies illustrate high return on the modest investment of addressing this often-ignored segment of the HCV-infected population (Martin, 2013b). These conclusions were drawn before the introduction of the latest DAA regimens. Conversely, there are no data to support the utility of pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from therapy. Scaling up HCV treatment in persons who inject drugs is necessary to positively impact the HCV epidemic in the US and globally.

HIV-Infected Men Who Have Sex With Men

Since 2000, a dramatic increase in incident HCV infections among HIV-infected men who have sex with men (MSM) who did not report IDU as a risk factor has been demonstrated in several US cities (van de Laar, 2010); (Samandari, 2017). Recognition and treatment of HCV infection (including acute infection) in this population may represent an important step in preventing subsequent infections (Martin, 2016). As with persons who inject drugs, HIV/HCV-coinfected MSM who engage in ongoing high-risk sexual practices should be treated for their HCV infection in conjunction with continued education about risk-reduction strategies. In particular, safer-sex strategies should be emphasized given the high rate of reinfection after SVR, which may approach 30% over 2 years in HIV-infected MSM with acute HCV infection (Lambers, 2011).

Incarcerated Persons

Among incarcerated individuals, the rate of HCV seroprevalence ranges from 30% to 60% (Post, 2013) and the rate of acute infection is approximately 1% (Larney, 2013). Screening for HCV infection is relatively uncommon in state prison

systems. Treatment uptake has historically been limited, in part because of the toxic effects and long treatment duration of older interferon-based therapies as well as concerns about cost (Spaulding, 2006). In particular, truncation of HCV treatment owing to release from prison has been cited as a major limitation to widespread, effective HCV treatment in correctional facilities (Post, 2013); (Chew, 2009). Shorter HCV treatment duration with DAAs reduces stay-related barriers to HCV treatment in prisons. Likewise, the improved safety of DAA regimens diminishes concerns about toxic effects. Coordinated treatment efforts within prison systems would likely rapidly decrease the prevalence of HCV infection in this at-risk population (He, 2016), although research is needed in this area.

Persons on Hemodialysis

The prevalence rate of HCV infection is markedly elevated in persons on hemodialysis, ranging from 2.6% to 22.9% in a large multinational study (Fissell, 2004). Studies in the US found a similarly elevated prevalence rate of 7.8% to 8.9% (CDC, 2001); (Finelli, 2005). Importantly, the seroprevalence of HCV was found to increase with time on dialysis, suggesting that nosocomial transmission, among other risk factors, plays a role in HCV acquisition in these patients (Fissell, 2004). Improved education and strict adherence to universal precautions can drastically reduce nosocomial HCV transmission risk for persons on hemodialysis (Jadoul, 1998), but clearance of HCV viremia through treatment-induced SVR eliminates the potential for transmission.

HCV-infected persons on hemodialysis have a decreased quality of life and increased mortality compared with those who are uninfected (Fabrizi, 2002); (Fabrizi, 2007); (Fabrizi, 2009). HCV infection in this population also has a deleterious impact on kidney transplantation outcomes with decreased patient and graft survival (Fabrizi, 2014). The increased risk for nosocomial transmission and the substantial clinical impact of HCV infection in those on hemodialysis are compelling arguments for HCV therapy as effective antiviral regimens that can be used in persons with advanced renal failure are now available (see Patients with Renal Impairment).

Patients Unlikely to Benefit From HCV Treatment

Patients with a limited life expectancy that cannot be remediated by HCV treatment, liver transplantation, or another directed therapy do not require antiviral treatment. Patients with a short life expectancy owing to liver disease should be managed in consultation with an expert. Chronic hepatitis C is associated with a wide range of comorbid conditions (Butt, 2011); (Louie, 2012). Little evidence exists to support initiation of HCV treatment in patients with a limited life expectancy (<12 months) owing to nonliver-related comorbid conditions. For these patients, the benefits of HCV treatment are unlikely to be realized and palliative care strategies should take precedence (Holmes, 2006); (Maddison, 2011).

Pretreatment Assessment

Recommendation for Pretreatment Assessment

RECOMMENDED	RATING
Evaluation for advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended for all persons with HCV infection, to facilitate decision making regarding HCV treatment strategy and to determine the need for initiating additional measures for the management of cirrhosis (eg, hepatocellular carcinoma screening) (see HCV Testing and Linkage to Care).	I, A

An accurate assessment of fibrosis remains vital as the degree of hepatic fibrosis is one of the most robust prognostic factors used to predict HCV disease progression and clinical outcomes (Everhart, 2010). Individuals with severe fibrosis require surveillance monitoring for liver cancer, esophageal varices, and hepatic function (Garcia-Tsao, 2007); (Bruix, 2011). In some instances, the recommended duration of treatment is also longer.

Although liver biopsy is the diagnostic standard, sampling error and observer variability limit test performance, particularly when inadequate sampling occurs. Up to one-third of bilobar biopsies had a difference of at least 1 stage between the lobes (Bedossa, 2003). In addition, the test is invasive and minor complications are common, limiting patient and practitioner acceptance. Although rare, serious complications such as bleeding are well recognized.

Noninvasive tests to stage the degree of fibrosis in patients with chronic HCV infection include models incorporating indirect serum biomarkers (routine tests), direct serum biomarkers (components of the extracellular matrix produced by activated hepatic stellate cells), and vibration-controlled transient liver elastography. No single method is recognized to have high accuracy alone, and each test must be interpreted carefully. A publication from the Agency for Healthcare Research and Quality found evidence in support of a number of blood tests; however, at best, they are only moderately useful for identifying clinically significant fibrosis or cirrhosis (Selph, 2014).

Vibration-controlled transient liver elastography is a noninvasive way to measure liver stiffness and correlates well with measurement of substantial fibrosis or cirrhosis in patients with chronic HCV infection. The measurement range, however, overlaps between stages (Ziol, 2005); (Afdhal, 2015); (Castera, 2005).

The most efficient approach to fibrosis assessment is to combine direct biomarkers and vibration-controlled transient liver elastography (Boursier, 2012); (European Association for the Study of the Liver and Asociacion Latinoamericana para el Estudio del Higado, 2015). A biopsy should be considered for any patient who has discordant results between the 2 modalities that would affect clinical decision making (eg, one shows cirrhosis and the other does not). The need for liver biopsy with this approach is markedly reduced.

Alternatively, if direct biomarkers or vibration-controlled transient liver elastography are not available, the AST-to-platelet ratio index (APRI) or fibrosis-4 (FIB-4) index score can prove helpful—although neither is sensitive enough to rule out substantial fibrosis (Sebastiani, 2009); (Castera, 2010); (Chou, 2013). Biopsy should be considered for those in whom more accurate fibrosis staging would impact treatment decisions. Individuals with clinically evident cirrhosis do not require additional staging (biopsy or noninvasive assessment).

Recommendation for Repeat Liver Disease Assessment	
RECOMMENDED	RATING
Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.	I, C

Ongoing assessment of liver disease is especially important in patients for whom therapy has been deferred. In line with evidence-driven recommendations for treatment of nearly all HCV-infected patients, several factors must be taken into consideration if treatment deferral is entertained or mandated by lack of medication access. As noted, strong and accumulating evidence argue against deferral because of decreased all-cause morbidity and mortality, prevention of onward transmission, and quality-of-life improvements for patients treated regardless of baseline fibrosis. Additionally, treatment of HCV infection may improve or prevent extraheptatic complications, including diabetes mellitus, cardiovascular disease, renal disease, and B-cell non-Hodgkin lymphoma (Conjeevaram, 2011); (Hsu, 2015); (Torres, 2015), which are not tied to fibrosis stage (Allison, 2015); (Pelta, 2016). Deferral practices based on fibrosis stage alone are inadequate and shortsighted.

Fibrosis progression varies markedly between individuals based on host, environmental, and viral factors (Table 1); (Feld, 2006). Fibrosis may not progress linearly. Some individuals (often those aged >50 years) may progress slowly for many years followed by an acceleration of fibrosis progression. Others may never develop substantial liver fibrosis despite longstanding infection. The presence of existing fibrosis is a strong risk factor for future fibrosis progression. Fibrosis

results from chronic hepatic necroinflammation; thus, a higher activity grade on liver biopsy and higher serum transaminase values are associated with more rapid fibrosis progression (Ghany, 2003). However, even patients with normal ALT levels may develop substantial liver fibrosis over time (Pradat, 2002); (Nutt, 2000). The limitations of transient elastography and liver biopsy in ascertaining the progression of fibrosis must be recognized.

Host factors associated with more rapid fibrosis progression include male sex, longer duration of infection, and older age at the time of infection (Poynard, 2001). Many patients have concomitant nonalcoholic fatty liver disease. The presence of hepatic steatosis (with or without steatohepatitis) on liver biopsy, elevated body mass index, insulin resistance, and iron overload are associated with fibrosis progression (Konerman, 2014); (Everhart, 2009). Chronic alcohol use is an important risk factor because alcohol consumption has been associated with more rapid fibrosis progression (Feld, 2006). A safe amount of alcohol consumption has not been established. Cigarette smoking may also lead to more rapid fibrosis progression. For more counseling recommendations, see Testing and Linkage to Care.

Immunosuppression leads to more rapid fibrosis progression, particularly in the settings of HIV/HCV coinfection and solid organ transplantation (Macias, 2009); (Konerman, 2014); (Berenguer, 2013). Therefore, immunocompromised patients should be treated even if they have mild liver fibrosis at presentation.

Level of HCV RNA does not correlate with stage of disease (degree of inflammation or fibrosis). Available data suggest that fibrosis progression occurs most rapidly in patients with genotype 3 infection (Kanwal, 2014); (Bochud, 2009). Aside from coinfection with HBV or HIV, no other viral factors are consistently associated with disease progression.

Although an ideal interval for assessment has not been established, annual evaluation is appropriate to discuss modifiable risk factors and update testing for hepatic function and markers for disease progression. For all individuals with advanced fibrosis, liver cancer screening dictates a minimum of evaluation every 6 months.

Table. Factors Associated With Accelerated Fibrosis Progression

Host	Viral
Nonmodifiable • Fibrosis stage • Inflammation grade • Older age at time of infection • Male sex • Organ transplant **Modifiable** • Alcohol consumption • Nonalcoholic fatty liver disease • Obesity • Insulin resistance	• Genotype 3 infection • Coinfection with hepatitis B virus or HIV

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Overview of Cost, Reimbursement, and Cost-Effectiveness Considerations for Hepatitis C Treatment Regimens

The hepatitis C guidance describes diagnosis, linkage to care, and treatment for people with HCV infection (AASLD/IDSA, 2017). However, reduced access to treatment is a common challenge due to restrictions on drug reimbursement. This section summarizes the US payer system, explains the concepts of cost, price, cost-effectiveness, value, and affordability, and addresses the cost-effectiveness of HCV treatment access. Although these terms may sound similar, the following discussion seeks to clarify them with regard to HCV therapy. This section aims to be informational. As explained, actual costs are rarely known. Accordingly, the HCV guidance does not utilize cost-effectiveness analysis to guide recommendations at this time.

Drug Cost and Reimbursement

Many organizations are involved with hepatitis C drug distribution and each can impact costs as well as decisions about which regimens are reimbursed (US GAO, 2015); (US CBO, 2015). The roles these organizations have in determining the actual price paid for drugs and who has access to treatment include the following:

- Pharmaceutical companies determine the wholesale acquisition cost (WAC) of a drug (analogous to a sticker price). The company negotiates contracts with other organizations within the pharmaceutical supply chain that allow for rebates or discounts to decrease the actual price paid.
- Pharmacy benefit managers (PBMs) act as intermediaries between pharmaceutical companies and health insurance companies. They negotiate contracts that may include restrictions on the types of providers or patients who can be reimbursed for treatment. They might also offer exclusivity (restrictions on which medications can be prescribed) in exchange for lower negotiated prices, often provided in the form of WAC discounts.
- Private insurance companies often have separate pharmacy and medical budgets and use PBMs or directly negotiate drug pricing with pharmaceutical companies. Insurance companies determine formulary placement, which impacts the choice of regimens and out-of-pocket expenses for patients. An insurance company can cover private, managed care Medicaid, and Medicare plans and have different formularies for each line of business.
- Medicaid is a heterogeneous consortium of insurance plans that includes fee-for-service and managed care options. Most plans negotiate rebates with pharmaceutical manufacturers (through PBMs or individually). For single-source drugs such as all-oral HCV treatments, Medicaid plans receive the lowest price offered to any other payer (outside of certain government agencies), and the minimum Medicaid drug rebate is 23.1% of the average manufacturer price (AMP). Differences in negotiated contracts between plans have led to Medicaid patients in different states having widely varied access to HCV therapy (Barua, 2015); (Canary, 2015); (Lo Re, 2016). State Medicaid programs have benefited from the Patient Protection and Affordable Care Act (ACA), although such benefits are mitigated in states that have opted out of expanding Medicaid coverage under the ACA. As the price of HCV therapies has decreased, some states have loosened their Medicaid treatment restrictions with a growing number providing treatment to all infected persons. Most states, however, continue to restrict access to HCV treatment based on stage of liver fibrosis or history of recent drug use. Proposed rollbacks of Medicaid expansion implemented under the ACA threaten to reduce insurance coverage among HCV-infected people and could lead to new treatment restrictions.
- Medicare covers HCV drugs through part D benefits and is prohibited by law from directly negotiating drug prices. These drug plans are offered through PBMs or commercial health plans, which may negotiate discounts or rebates with pharmaceutical companies.
- The Veterans Health Administration receives mandated rebates through the Federal Supply Schedule program, which sets drug prices for several government agencies (including the Department of Veterans Affairs, federal prisons, and the Department of Defense) and typically receives substantial discounts over average wholesale price (AWP).
- State prisons and jails are usually excluded from Medicaid-related rebates and often do not have the negotiating leverage of larger organizations and, therefore, may pay higher prices than most other organizations.

- Specialty pharmacies receive dispensing fees and may receive additional payments from contracted insurance companies, PBMs, or pharmaceutical companies to provide services such as adherence support and/or management of adverse effects, and outcome measurements, such as early discontinuation rates and sustained virologic response rates.
- Patients incur costs (eg, copayment or coinsurance) determined by their pharmacy plan. Patient assistance programs offered by pharmaceutical companies or foundations can cover many of these out-of-pocket expenses or provide drugs at no cost to qualified patients who are unable to pay.

Except for mandated rebates, negotiated drug prices are considered confidential business contracts. Therefore, there is almost no transparency regarding the actual prices paid for hepatitis C drugs (Saag, 2015). However, the average negotiated discount of 22% in 2014 increased to 46% less than the WAC in 2015, implying that many payers are paying well below the WAC for HCV medications (Committee on Finance US Senate, 2016).

Cost-Effectiveness

Cost-effectiveness analysis (CEA) compares the relative costs and outcomes of 2 or more interventions. CEA explicitly recognizes budget limitations for healthcare spending and seeks to maximize public health benefits within those budgetary constraints. The core question that CEA addresses is whether to invest limited healthcare dollars in a new treatment/therapy, or use that money to invest in another healthcare intervention that would provide better outcomes for the same monetary investment. The focus of CEA is, therefore, not simply cost or saving money but health benefits. It assumes that all available resources will be spent and provides a framework for prioritizing among available treatment options by formally assessing the comparative costs and health benefits accrued from a new treatment relative to current treatment.

The cost-effectiveness of a treatment is typically expressed as an incremental cost-effectiveness ratio (ICER).

$$\frac{\text{cost new treatment - cost current treatment}}{\text{benefit new treatment - benefit current treatment}}$$

Estimating and interpreting the ICER requires that we answer three questions:

1. *How much more money will be spent with the new treatment versus the old treatment?*
   The additional cost of new treatment includes that of new medications as well as the costs that will be avoided by preventing disease complications. Prevention of long-term complications is especially important when considering the cost-effectiveness of HCV treatments because the costs of the therapy are immediate, while those avoided by preventing advanced liver disease and other complications of chronic infection often accrue years in the future.

2. *How much more benefit will occur with the new versus the old treatment?*
   Life expectancy is a valuable measure of benefit, but considering only mortality benefits fails to recognize the value of treatments that improve quality of life. The quality-adjusted life-year (QALY) provides a measure that integrates both longevity and quality of life and is the preferred outcomes for CEA.

3. *How is the ICER to be interpreted?*
   The ideal CEA would list every possible healthcare intervention, its lifetime medical cost, and QALYs lived. Such a list would allow for perfect theoretical prioritization of spending to maximize QALY across the population. In reality, CEA compares the ICER for a specific treatment to a threshold value and rejects treatments with an ICER exceeding a particular threshold as not being cost-effective. The threshold value is referred to as the societal willingness-to-pay threshold. It is not meant to be a valuation of how much society is willing to pay to save a life. Rather, it is meant to reflect the average return in QALY expected if the available budget was not used to provide a new treatment but instead invested into the current healthcare system. In the United States, the willingness-to-pay threshold is typically considered to be $50,000 or $100,000/QALY gained.

Affordability

An intervention that is cost-effective is not necessarily affordable. Affordability refers to whether a payer has sufficient resources in its annual budget to pay for a new therapy for all who might need or want it within that year. Several characteristics of CEA limit its ability to speak to the budgetary impact of interventions being implemented in the real world.

1. *Perspective on cost*
   CEA seeks to inform decisions about how society should prioritize healthcare spending. As such, it typically assumes a societal perspective on costs and includes all costs from all payers, including out-of-pocket expenses for the patient. When making coverage decisions for therapy, however, an insurer considers only its own revenues and expenses.

2. *Time horizon*
   CEA uses a lifetime time horizon, meaning it considers lifetime costs and benefits, including those that occur in the distant future. Business budget planning, however, typically assumes a 1-year to 5-year perspective. Savings that may accrue 30 years from now have no impact on spending decisions today because they have little bearing on the solvency of the current budget.

3. *Weak association between willingness to pay and the real-world bottom line*
   Societal willingness-to-pay thresholds in CEAs are not based on actual budget calculations and have little relationship to a payer's bottom line. Willingness to pay is meant to be an estimate of the opportunity cost of investing in a new therapy. In economics, opportunity cost refers to how else that money could have been spent and the benefits lost from not investing in that alternative. When payers make a decision about coverage, the calculation is more straightforward and relates to the short-term cost of medications and the budgetary impact. Given the rapid development of new technologies and therapies, funding all of them (even if they all fell below the societal willingness-to-pay threshold) would likely lead to uncontrolled growth in demand and exceed the limited healthcare budget.

There is no formula that provides a good means of integrating the concerns of value and affordability. When new therapies for HCV are deemed cost-effective, it indicates that these therapies provide good benefit for the resources invested, and providing such therapy to more people would be a good long-term investment. Determining the total resources that can be spent on HCV treatment, however, depends on political and economic factors that are not captured by cost-effectiveness determinations.

Cost-Effectiveness of Current Direct-Acting Antiviral Regimens for Hepatitis C Treatment

Since the first direct-acting antivirals (DAAs) received US Food and Drug Administration approval in 2011, several cost-effectiveness investigations have compared DAA-based regimens to previous standard-of-care regimens to calculate ICERs. They have also investigated the cost-effectiveness of eliminating HCV treatment restrictions. Compared to interferon-based regimens, the ICER for DAAs has consistently been estimated at <$100,000/QALY for all genotypes and fibrosis stages.

Several studies have compared DAA regimens against one another. In general, when given a choice between recommended HCV DAA regimens, the less costly regimen is preferred as a more efficient use of resources (even if it requires multiple tablet dosing). Because of the similar efficacy of most DAA regimens, cost becomes the critical factor driving cost-effectiveness. Recent studies have also estimated the cost-effectiveness of HCV treatment in special populations, including patients awaiting liver transplantation, HIV/HCV coinfected patients, those with chronic kidney disease, and persons who inject drugs—all with favorable ICERs. At this time, it is reasonable to conclude that DAA regimens provide good value for the resources invested.

Cost vs Affordability for HCV Treatment

Despite a growing body of evidence that HCV treatment is cost-effective and may even be cost saving over the long term in some cases, many US payers—especially those offering Medicaid insurance products—continue to limit access to HCV treatment. Access has improved as cost has decreased but limitations remain. Proposed reductions in healthcare spending for Medicaid would likely exacerbate the problem as the value of the HCV medications would remain unchanged but the resources available to provide them would shrink.

Conclusions

Several recent studies have demonstrated the economic value of HCV treatment and made it clear that HCV therapy is cost-effective (Chahal, 2016); (Chatwal, 2015); (Chidi, 2016); (Linas, 2015); (Martin, 2016a); (Najafzadeh, 2015); (Rein, 2015); (Tice, 2015); (Youmossi, 2015a). The high cost of these medications combined with the high prevalence of disease has led to limiting access for some patients. The issue is complex. Although the wholesale acquisition costs of HCV drugs often make treatment appear unaffordable, the reality is that insurers, PBMs, and government agencies negotiate pricing and few actually pay this much-publicized price. Negotiated pricing and cost structure for pharmaceutical products in the US are not transparent, however. Thus, it is therefore difficult to estimate the true budgetary impact of providing HCV drugs. Competition and negotiated pricing have reduced prices but cost continues to limit the public health impact of new DAA therapies. Insurers, government, and pharmaceutical companies should work together to bring medication prices to the point where all persons in need of treatment are able to afford and readily access it.

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Monitoring Patients Who Are Starting HCV Treatment, Are on Treatment, or Have Completed Therapy

This section provides guidance on monitoring patients with chronic hepatitis C who are starting treatment, are on treatment, or have completed treatment. The section is divided into 3 parts: pretreatment and on-treatment monitoring; post-treatment follow-up for persons in whom treatment has failed to clear the virus; and post-treatment follow-up for those who achieved a sustained virologic response (SVR; virologic cure).

Pretreatment and On-Treatment Monitoring

Recommended Assessments Prior to Starting Antiviral Therapy	
RECOMMENDED	RATING
Staging of hepatic fibrosis is essential prior to HCV treatment (see Testing and Linkage to Care and see When and in Whom to Treat). Assessment of potential drug-drug interactions with concomitant medications is recommended prior to starting antiviral therapy. • Patients should also be educated about the proper administration of medications (eg, dose, frequency of medicines, food effect, missed doses, adverse effects, etc), the crucial importance of adherence, and the necessity for close supervision and blood tests during and after treatment. **The following laboratory tests are recommended within 12 weeks prior to starting antiviral therapy:** • Complete blood count (CBC) • International normalized ratio (INR) • Hepatic function panel (ie, albumin, total and direct bilirubin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], and alkaline phosphatase levels) • Calculated glomerular filtration rate (eGFR) **The following laboratory tests are recommended at any time prior to starting antiviral therapy:** • HCV genotype and subtype • Quantitative HCV RNA (HCV viral load)	I, C
Patients scheduled to receive an HCV NS3 protease inhibitor (ie, paritaprevir, simeprevir, grazoprevir, voxilaprevir, glecaprevir) should be assessed for a history of decompensated liver disease and for liver disease severity using the Child-Turcotte-Pugh (CTP) score (see third-party calculator). • Patients with current or prior history of decompensated liver disease or with a current CTP	I, A

Recommended Assessments Prior to Starting Antiviral Therapy	
score ≥7 should **not** receive treatment with regimens that contain NS3 protease inhibitors due to increased blood levels and/or lack of safety data. • Similarly, patients with a CTP score of 5 or 6 who cannot be closely monitored for laboratory or clinical symptoms during treatment should **not** receive treatment with a regimen that contains paritaprevir/ritonavir.	
All patients initiating HCV direct-acting antiviral (DAA) therapy should be assessed for HBV coinfection with HBsAg testing, and for evidence of prior infection with anti-HBs and anti-HBc testing.	IIa, B
Testing for the presence of resistance-associated substitutions (RASs) prior to starting treatment should be performed as recommended in the Initial Treatment and the Retreatment sections.	IIb, B

Recommended Monitoring During Antiviral Therapy	
RECOMMENDED	RATING [1]
Clinic visits or telephone contact are recommended as clinically indicated during treatment to ensure medication adherence, and to monitor for adverse events and potential drug-drug interactions with newly prescribed medications.	I, B
Complete blood count (CBC), creatinine level, calculated glomerular filtration rate (eGFR), and a hepatic function panel are recommended after 4 weeks of treatment and as clinically indicated. More frequent assessment for drug-related adverse effects (eg, CBC for patients receiving ribavirin) is recommended as clinically indicated. Patients receiving elbasvir/grazoprevir should be monitored with a hepatic function panel at 8 weeks (and again at 12 weeks if receiving 16 weeks of treatment).	I, B
A 10-fold increase in alanine aminotransferase (ALT) activity at any time during treatment should prompt discontinuation of therapy. An increase in ALT <10-fold that is accompanied by any weakness, nausea, vomiting, jaundice, or significantly increased bilirubin, alkaline phosphatase, or international normalized ratio (INR) should also prompt discontinuation of therapy. Asymptomatic increases in ALT <10-fold should be closely monitored with repeat testing at 2-week intervals. If levels remain persistently elevated, consideration should be given to discontinuation of therapy.	I, B
Quantitative HCV viral load testing is recommended after 4 weeks of therapy and 12 weeks after completion of therapy. Antiviral drug therapy should **not** be interrupted or discontinued if HCV RNA levels are not performed or available during treatment.	I, B

Recommended Monitoring During Antiviral Therapy	
Quantitative HCV viral load testing can be considered at the end of treatment and 24 weeks or longer following the completion of therapy.	I, B
Patients with compensated cirrhosis[a] who are receiving paritaprevir/ritonavir-based regimens should be assessed for clinical signs of decompensated liver disease (eg, ascites, encephalopathy, or serum bilirubin >3 mg/dL) and for biochemical evidence of liver injury with a hepatic function panel at week 2 and week 4 of treatment, and as needed during the remainder of treatment. Paritaprevir/ritonavir-based regimens should be discontinued if a patient develops ascites, encephalopathy, or a significant increase in direct bilirubin, ALT, or AST.	I, A
For HBsAg-positive patients who are not already on HBV suppressive therapy, the following are recommended: • For patients whose HBV DNA level meets AASLD criteria for treatment, antiviral therapy for HBV should be initiated. • For patients whose baseline HBV DNA level does not meet criteria for treatment, one of two approaches may be taken: ◦ Initiate prophylactic antiviral therapy for those with low or undetectable HBV DNA levels. If this course is elected, pending further data, prophylaxis should be continued until 12 weeks after completion of DAA therapy. ◦ Monitor HBV DNA levels during and immediately after DAA therapy for HCV. Antiviral treatment for HBV should be given in the event of a rise in HBV DNA >10-fold above baseline or to >1000 IU/mL in those with a previously undetectable or unquantifiable HBV DNA level.	IIa, B
[a] For decompensated cirrhosis, please refer to the appropriate section.	

Recommendations for Discontinuation of Treatment Because of Lack of Efficacy	
RECOMMENDED	RATING
If HCV RNA is detectable at week 4 of treatment, repeat quantitative HCV RNA viral load testing is recommended after 2 additional weeks of treatment (treatment week 6). If quantitative HCV viral load has increased by >10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week 6 (or thereafter), discontinuation of HCV treatment is recommended.	III, C
The significance of a positive HCV-RNA test result at week 4 that remains positive but lower at week 6 is unknown. No recommendation to stop therapy or extend therapy can be provided at this time.	III, C

Recommended Monitoring for Pregnancy-Related Issues Prior to and During Antiviral Therapy That Includes Ribavirin	
RECOMMENDED	RATING [1]
Women of childbearing age should be counseled not to become pregnant while receiving a ribavirin-containing antiviral regimen, and for at least 6 months after stopping the regimen.	I, C
Male partners of women of childbearing age should be cautioned to prevent pregnancy while they are receiving a ribavirin-containing antiviral regimen, and for up to 6 months after stopping the regimen.	I, C
Serum pregnancy testing is recommended for women of childbearing age prior to beginning treatment with a regimen that includes ribavirin.	I, C
Since the safety of DAA regimens that do not include ribavirin has not been established during pregnancy, counseling and serum pregnancy testing should be offered to women of childbearing age before beginning HCV treatment.	I, C
Assessment of contraceptive use and of possible pregnancy is recommended at appropriate intervals during (and for 6 months after) ribavirin treatment for women of childbearing potential, and for female partners of men who receive ribavirin treatment.	I, C

The pretreatment testing described assumes that a decision to treat with antiviral medications has already been made and that the testing involved in deciding to treat—including testing for HCV genotype and assessment of hepatic fibrosis—has already been completed (see When and in Whom to Initiate HCV Therapy).

Prior to starting treatment, patients should be evaluated for potential drug-drug interactions with selected antiviral medications by consulting the prescribing information and using other resources (eg, http://www.hep-druginteractions.org). The table below lists known drug-drug interactions between HCV DAAs and selected medications.

Table. Drug Interactions with Direct-Acting Antivirals and Selected Concomitant Medications
X = Assess potential drug interaction. Hover over column labels for complete treatment name.

Concomitant Medications	DCV	LDV	PrOD	SMV	SOF	EBV/GRZ	VEL
Acid-reducing agents[a]		X	X				X
Alfuzosin/tamsulosin			X				
Amiodarone	X	X	X	X	X		X
Anticonvulsants[a]	X	X	X	X	X	X	X
Antiretrovirals[a]	See HIV section						
Azole antifungals[a]	X[b]		X	X		X	
Buprenorphine/naloxone			X				
Calcineurin inhibitors[a]			X	X		X	
Calcium channel blockers[a]	X		X	X		X	
Cisapride			X	X		X	
Digoxin	X	X		X		X	
Ergot derivatives			X				
Ethinyl estradiol–containing products			X				
Furosemide			X				
Gemfibrozil			X				
Glucocorticoids[a]	X		X (inhaled, intranasal)	X		X	
Herbals St. John's wort Milk thistle	X	X	X	 X X	X	X X	X
HMG-CoA reductase inhibitors (statins)[a]	X	X	X	X		X	
Macrolide antimicrobials[a]	X[b]			X		X	
Other antiarrythmics[a]			X	X		X	
Phosphodiesterase inhibitors[a]			X	X		X	
Pimozide			X				
Rifamycin antimicrobials[a]	X	X	X	X	X	X	X
Salmeterol			X				
Sedatives[a]			X	X		X	

[a] Some drug interactions are not class specific; see product prescribing information for specific drugs within a class.
[b] Requires a daclatasvir dose modification

The education of patients and caregivers about potential adverse effects of therapy and their management is an integral component of treatment and is important for a successful outcome in all patient populations. During treatment, individuals should be followed at clinically appropriate intervals to ensure medication adherence, assess adverse events and potential

drug-drug interactions, and monitor blood test results necessary for patient safety. The frequency and type of contact (eg, clinic visit, phone call, etc) are variable but need to be sufficient to assess patient safety and response to treatment, as outlined above.

The assessment of HCV viral load at week 4 of therapy is useful to determine initial response to therapy and adherence. In phase 3 clinical trials, almost all patients who did not have cirrhosis had an undetectable HCV RNA level at week 4. Those with cirrhosis may require more than 4 weeks of treatment before the HCV RNA level is undetectable. There are minimal data on how to use the HCV RNA level during treatment to determine when to stop treatment for futility. The current recommendation to repeat quantitative HCV RNA testing at week 6 of treatment and to discontinue treatment if the quantitative HCV RNA level increases by >10-fold (>1 $\log_{10}$ IU/mL) is based on expert opinion. There are no data to support stopping treatment based on detectable HCV RNA at weeks 2, 3, or 4 of treatment, or that detectable HCV RNA at these time points signifies medication nonadherence.

Although HCV RNA testing is recommended at week 4 of treatment, failure to test for HCV RNA at week 4 is not a reason to discontinue therapy. HCV RNA assessment at the end of treatment allows for the differentiation of relapse from nonresponse/breakthrough for patients who fail to achieve SVR. Nevertheless, testing for HCV RNA at the end of treatment is optional. On the other hand, it is essential to test for HCV RNA 12 weeks (or longer) after treatment completion. Undetectable or unquantifiable HCV RNA 12 weeks or longer after treatment completion is defined as a sustained virologic response (SVR), which is consistent with cure of hepatitis C infection. Virologic relapse is rare 12 weeks or longer after treatment completion. Nevertheless, repeat quantitative HCV-RNA testing can be considered at 24 or more weeks after completing treatment for patients in whom ALT increases to above the upper limit of normal.

During clinical trials with elbasvir/grazoprevir, with or without ribavirin, 1% of subjects experienced ALT elevations from normal levels to >5 times the upper limit of normal, generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing therapy or completion of therapy. Higher rates of late ALT elevations occurred in females, those of Asian descent, and patients aged ≥65 years. Hepatic laboratory testing should be performed prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12 (Zepatier Package Insert, 2017).

Patients with compensated cirrhosis (Child's A) who are receiving a paritaprevir/ritonavir-based regimen should be followed closely. Please see recommendation above and the statement on the FDA warning regarding use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Patients being treated with amiodarone should not receive sofosbuvir-based regimens due to risk of life-threatening arrhythmias. Because of its long half-life, it is advised that persons should be off amiodarone for at least 6 months before initiating sofosbuvir. If the decision is made to start sofosbuvir in this setting, continued vigilance for bradycardia should be exercised.

Pregnancy

Ribavirin causes fetal death and fetal abnormalities in animals. Thus, it is imperative for persons of childbearing potential who receive ribavirin to use at least 2 reliable forms of effective contraception during treatment and for a period of 6 months thereafter. It is recommended that the healthcare practitioner document the discussion of the potential teratogenic effects of ribavirin in the patient's medical record. Ethinyl estradiol-containing contraceptives should be avoided in those receiving paritaprevir/ritonavir/ombitasvir plus dasabuvir due to the risk of developing elevated transaminase levels.

No adequate human data are available to establish whether DAAs pose a risk to pregnancy outcomes. It is recommended that female patients have a thorough discussion of potential pregnancy-related drug effects prior to starting antiviral treatment. Given the relatively short duration of treatment and the potential to use ribavirin-free regimens in most patients, the potential risks and benefits of delaying pregnancy until HCV antiviral treatment is completed should be considered. For additional information on HCV and pregnancy, click here.

Reactivation of HBV

Cases of HBV reactivation, occasionally fulminant, during or after DAA therapy have been reported in HBV/HCV coinfected patients who were not receiving HBV suppressive therapy (Hayashi, 2016); (Takayama, 2016); (Ende, 2015); (Collins, 2015); (De Monte, 2016); (Sulkowski, 2016); (Wang, 2016); (Bersoff-Matcha, 2017). In light of these observations and consistent with general recommendations for the assessment of the HCV-infected patient, all patients initiating HCV DAA therapy should be assessed for HBV coinfection with HBsAg testing, and for prior infection with anti-HBs and anti-HBc testing. HBV vaccination is recommended for all susceptible individuals. A test for HBV DNA should be obtained prior to DAA therapy in patients who are HBsAg positive. HBsAg positivity does not represent a contraindication to HCV DAA therapy. Patients meeting criteria for treatment of active HBV infection should be started on therapy at the same time (or before) HCV DAA therapy is initiated (Terrault, 2015).

Patients with low or undetectable HBV DNA levels can either receive prophylactic treatment for HBV for the duration of the DAA treatment to SVR12 or be monitored at regular intervals (usually not more frequently than every 4 weeks) for HBV reactivation with HBV-DNA testing. If monitoring is elected, HBV treatment should be started if the HBV DNA level increases >10-fold or is >1000 IU/mL in a patient with undetectable or unquantifiable HBV DNA prior to DAA treatment. There are insufficient data to provide clear recommendations for the monitoring of HBV DNA among patients testing positive either for anti-HBc alone (isolated anti-HBc) or for anti-HBs and anti-HBc (immune recovery). However, the possibility of HBV reactivation should be considered in these patients in the event of an unexplained increase in liver enzymes during and/or after completion of DAA therapy.

Post-Treatment Follow-Up for Patients in Whom Treatment Failed

Recommended Monitoring for Patients in Whom Treatment Failed to Achieve a Sustained Virologic Response	
RECOMMENDED	RATING
Disease progression assessment every 6 to 12 months with a hepatic function panel, complete blood count (CBC), and international normalized ratio (INR) is recommended.	I, C
Screening for hepatocellular carcinoma with ultrasound examination every 6 months is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4).	I, C
Endoscopic screening for esophageal varices is recommended if cirrhosis[a] is present.	I, A
Evaluation for retreatment is recommended as effective alternative treatments become available.	I, C
[a] For decompensated cirrhosis, please refer to the appropriate section.	

The Following Monitoring Is Not Recommended During or After Therapy	
NOT RECOMMENDED	RATING
Monitoring for HCV drug resistance-associated substitutions during or after therapy is not recommended.	IIb, C

Patients who do not achieve SVR retain the possibility of continued liver injury and the potential to transmit HCV to others. Such patients should be monitored for progressive liver disease and considered for retreatment when alternative treatments are available (see Retreatment of Persons in Whom Prior Therapy Has Failed).

Given that persons in whom treatment failed remain at risk for ongoing liver injury and liver fibrosis progression (Dienstag, 2011), these patients should be monitored for signs and symptoms of cirrhosis. Patients in whom antiviral therapy failed may harbor viruses that are resistant to 1 or more of the antivirals at the time of virologic breakthrough (Lawitz, 2014a); (Schneider, 2014). However, there is no evidence to date that the presence of resistance-associated substitutions (RASs) results in more progressive liver injury than would have occurred if the patient did not have resistant viruses. Additional information about RASs is available in the HCV Resistance Primer section. If there remains uncertainty regarding the applicability of RAS testing, consultation with an expert in the treatment of HCV infection may be useful.

Information regarding retreatment of patients whose initial treatment regimen failed is available in the Retreatment section.

Post-Treatment Follow-Up for Patients Who Achieved a Sustained Virologic Response

Recommended Follow-Up for Patients Who Achieved a Sustained Virologic Response (SVR)

RECOMMENDED	RATING
For patients who do not have advanced fibrosis (ie, those with Metavir stage F0, F1, or F2), recommended follow-up is the same as if they were never infected with HCV.	I, B
Assessment for HCV recurrence or reinfection is recommended only if the patient has ongoing risk for HCV infection or otherwise unexplained hepatic dysfunction develops. In such cases, a quantitative HCV-RNA test rather than an HCV-antibody test is recommended to assess for HCV recurrence or reinfection.	I, A
Surveillance for hepatocellular carcinoma with twice-yearly ultrasound examination is recommended for patients with advanced fibrosis (ie, Metavir stage F3 or F4) who achieve SVR.	I, C
A baseline endoscopy is recommended to screen for varices if cirrhosis[a] is present. Patients in whom varices are found should be treated and followed as indicated.	I, C
Assessment of other causes of liver disease is recommended for patients who develop persistently abnormal liver tests after achieving SVR.	I, C

[a] For decompensated cirrhosis, please refer to the appropriate section.

Patients who have undetectable HCV RNA in the serum, as assessed by a sensitive polymerase chain reaction (PCR) assay, ≥12 weeks after treatment completion are deemed to have achieved SVR. In these patients, HCV-related liver injury stops, although they remain at risk for non-HCV–related liver disease, such as fatty liver disease or alcoholic liver disease. Patients with cirrhosis or advanced fibrosis remain at risk for developing hepatocellular carcinoma (HCC).

With the advent of highly effective HCV antiviral regimens, the likelihood of achieving SVR among adherent, immunologically competent, treatment-naive patients with compensated liver disease generally exceeds 95%. Among patients who achieved SVR with peginterferon/ribavirin treatment, more than 99% have remained free of HCV infection when followed for 5 years after treatment completion (Manns, 2013). Thus, achieving SVR is considered a virologic cure

of HCV infection.

SVR typically aborts progression of liver injury with regression of liver fibrosis in most, but not all, treated patients (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Because of lack of progression, patients without advanced liver fibrosis (ie, Metavir stage F0, F1, or F2) who achieve SVR should receive standard medical care that is recommended for patients who were never infected with HCV.

Among patients with advanced liver fibrosis (ie, Metavir stage F3 or F4) who achieve SVR, decompensated liver disease (with the exception of HCC) rarely develops during follow-up, and overall survival is prolonged (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Liver fibrosis and liver function test results improve in most patients who achieve SVR (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Bleeding from esophageal varices is rare after SVR (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). Patients with cirrhosis should receive routine surveillance endoscopy for detection of esophageal varices if not previously done; if varices are found, they should be treated or followed as indicated (Garcia-Tsao, 2007).

The risk of developing HCC among cirrhotic patients who receive DAA treatment is debated. Multiple studies of cirrhotic patients who achieved SVR with peginterferon/ribavirin reported a significant reduction in the risk of developing HCC (Morisco, 2013); (Morgan, 2010); (George, 2009); (Morgan, 2013); (Singal, 2010). A recent report suggested a higher than expected frequency of HCC in patients with HCV-related cirrhosis treated successfully with DAAs (Reig, 2016). However, a meta-analysis evaluating the incidence of HCC among persons achieving SVR with DAAs found that the risk of HCC did not exceed that seen in patients who experienced SVR with interferon-based treatment after adjustment for baseline risk factors for HCC (Waziry, 2017).

Patients with cirrhosis who achieve SVR remain at risk for HCC. Thus, they should continue to undergo regular surveillance for HCC despite the lowered risk that results after viral eradication (Bruix, 2011). The risk of HCC among patients with advanced fibrosis prior to treatment but who have regression to minimal fibrosis after treatment is not known. In the absence of data to the contrary, such patients remain at some risk for HCC and should be monitored at regular intervals for HCC. Alpha-fetoprotein (AFP) alone is considered an inadequate screening test for HCC (Bruix, 2011).

Patients in whom SVR is achieved but who have another potential cause of liver disease (eg, excessive alcohol use, metabolic syndrome with or without proven fatty liver disease, or iron overload) remain at risk for fibrosis progression. It is recommended that such patients be educated about the risk of liver disease and monitored for liver disease progression with periodic physical examination, blood tests, and potentially, tests for liver fibrosis by a liver disease specialist.

Patients who achieve SVR can be reinfected with HCV if they are re-exposed to the virus. Annual testing for HCV reinfection among patients with ongoing risk for HCV infection (eg, injection drug use or high-risk sexual exposure) is recommended. A flare in liver enzyme levels should prompt immediate evaluation for HCV reinfection (see Management of Acute HCV Infection). HCV antibody (anti-HCV) remains positive in most patients following SVR. Thus, testing for HCV reinfection using an assay that detects HCV RNA (ie, a quantitative HCV-RNA test) is recommended.

Monitoring for HCV During Chemotherapy and Immunosuppression	
NOT RECOMMENDED	RATING
Prospective monitoring for HCV recurrence among patients who achieved a sustained virologic response and are receiving immunosuppressive treatment (eg, systemic corticosteroids, antimetabolites, chemotherapy, etc) is **not** routinely recommended.	III, C

Acute liver injury is common among patients receiving chemotherapy or immunosuppressive agents. Testing for hepatitis viruses should be included in the laboratory assessment of the cause of liver injury in these patients. Approximately 23% of patients with active HCV infection—especially those with a hematologic malignancy—have a flare in their HCV RNA

level (>10-fold) during chemotherapy. An ALT level increase is less common and clinical symptoms of hepatitis are uncommon (Torres, 2017). Among patients who have recovered from hepatitis C, either spontaneously or with DAA treatment, reactivation of HCV (ie, detectable HCV RNA) during chemotherapy is distinctly uncommon and is not anticipated to occur since there is no residual reservoir for the virus. Thus, in this latter group, routine testing for HCV RNA during immunosuppressive treatment or prophylactic administration of antivirals during immunosuppressive treatment is not recommended.

Last update: September 21, 2017

HCV Resistance Primer

Introduction

Understanding principles of the emergence of drug-resistant viruses is critical when using targeted antiviral therapies. The best example of these principles can be gleaned from the study of HIV. Like HIV, HCV is an approximately 9.5 kilobase RNA virus that replicates very rapidly (billions of viruses daily). The production of each new virus is performed by an enzyme that results in 1 to 3 errors per replication cycle, on average. Many of these errors either have no effect on the progeny virus product or result in progeny viruses that are nonreplication competent (ie, dead viruses). For some newly produced viruses, however, the transcription errors result in changes in critical coding regions that may, by chance, change the susceptibility of the virus to 1 or more drugs used to treat the virus. The emergence of such drug-resistant viruses most often occurs when drug levels are subtherapeutic, thereby creating selective pressure for the resistant viruses to emerge as the dominant species. These newly formed resistant viruses have a selective growth advantage that allows them to replicate in the presence of antiviral drugs. In a subset of patients with chronic HCV infection, viral variants harboring substitutions associated with resistance to HCV directing-acting antivirals (DAAs) are detectable prior to antiviral therapy and, particularly in the case of NS5A inhibitor-containing regimens, may negatively impact treatment response. These substitutions often are referred to as baseline resistance-associated substitutions (RASs).

In the case of HCV DAAs, resistant viruses are also selected for and/or enriched in patients for whom a DAA regimen fails. These viruses contain substitutions that are designated as treatment-emergent (or treatment-selected) RASs. NS5A and NS3 RASs are frequently selected in patients with failure of NS5A or NS3 inhibitor-containing regimens, respectively. In contrast, NS5B nucleotide RASs are rarely detected (1% of failures) even after exposure to a failing DAA regimen containing a nucleotide inhibitor (Svarovskaia, 2014); (Wyles, 2017). This is likely due to the highly conserved catalytic site region that nucleotides bind, making substitutions in this region extremely rare—often referred to as a high barrier to resistance. Additionally, any such substitution would likely render the virus replication incompetent. Compounding the clinical impact of NS5A RASs is their ability to maintain high replication competence (aka, relative fitness) in the absence of continued drug pressure, allowing them to remain the dominant viral quasispecies for prolonged periods (years) relative to NS3 protease or NS5B nucleotide polymerase inhibitor RASs, which are typically less fit and tend to disappear over several months, being overcome by more fit wild-type virus species.

The magnitude of the negative impact of RASs, both baseline and selected, on treatment outcome varies according to regimen (coadministered drugs); patient factors that impact treatment response (cirrhosis); and the fold change decrease in potency conferred by the specific RAS(s). Given these considerations, RAS testing alone will not dictate optimal DAA regimen selection. In addition, a drug predicted to suffer a significant loss of potency in the presence of a RAS still may be used in specific clinical settings/regimens.

Terminology, Thresholds of Clinical Relevance, and Assays

Terminology

1. Naming Convention for Hepatitis C Proteins
   The hepatitis C genome codes for approximately 5 HCV-specific proteins, which are essential to: 1) form the viral structure (core and envelope proteins); 2) cut the HCV polyprotein; 3) provide enzymatic functions for replication and escape from the innate immune response (NS3/NS4A protease); 4) replicate the HCV RNA (NS5B RNA-dependent RNA polymerase); and 5) bind the HCV replication complex during replication and assembly (NS5A).

2. Polymorphism (Substitution)
   A reference (or consensus) nucleotide—and therefore amino acid sequence—has been defined for each HCV genotype. A polymorphism (or substitution) is a difference in an amino acid at a defined position of the HCV protein between a patient's HCV and the reference HCV protein. Substitution is the preferred terminology among most experts. However, the US Food and Drug Administration currently uses the term polymorphism.

To define a polymorphism, it is necessary to define: the HCV genotype (eg, genotype 1, 2, 3, etc) and subtype (eg, 1a vs 1b); the HCV protein (eg, NS5A); and the amino acid position (eg, 93). Polymorphisms are reported as letter-number-letter (eg, Y93H). The first letter refers to the amino acid typically expected for that position in the reference protein. The number refers to the amino acid position, and the final letter refers to the amino acid that is found in the patient's HCV isolate. Thus, NS5A Y93H refers to amino acid position 93 of the NS5A protein. The amino acid at this position in the reference strain is Y (ie, tyrosine) and the amino acid in the tested strain is H (ie, histidine). For some patients, multiple variants are present and several amino acids may be found at a given position. Thus, it is possible to have a virus with NS5A Y93H/M. Such a patient would have viruses with the amino acids histidine (H) or methionine (M) at position 93 of the NS5A protein.

3. Resistance-Associated Substitutions
   A resistance-associated substitution describes any amino acid change from the consensus sequence at a position that has been associated with reduced susceptibility of a virus to 1 or more antiviral drugs. A specific RAS may or may not confer a phenotypic loss of susceptibility to other/multiple antiviral agents.

4. Drug-Class RASs
   Drug-class RASs are amino acid substitutions that reduce the susceptibility of a virus to any (and at least 1) member of a drug class or, alternatively, the viral variants with reduced susceptibility that carry these substitutions. Class RASs may or may not confer resistance to a specific drug in that class.

5. Drug-Specific RASs
   Drug-specific RASs are amino acid substitutions that reduce the susceptibility of a virus to a specific drug. When assessing the potential clinical impact of RASs on a given regimen, drug-specific RASs should be used. In an HCV-infected population not previously exposed to a DAA drug or class, drug-specific RASs will be found less frequently than class RASs.

Thresholds of Clinical Relevance

HCV resistance to DAAs is a rapidly evolving field with demonstrated clinical impact in specific situations with currently available DAA regimens. Presently, the most clinically significant RASs are in the NS5A position for genotypes 1a and 3.

Data from clinical trials have demonstrated that RASs are commonly, but not always, found at the time of virologic failure. Viruses that are resistant to NS3/4A protease inhibitors seem to be less fit and may disappear from peripheral blood within a few weeks to months, whereas NS5A inhibitor-resistant viruses may persist for years, which could have implications for treatment and retreatment.

In general, drug-specific RASs need to be present in at least 15% of the viruses of a given patient to reduce the likelihood of achieving SVR (Pawlotsky, 2016). Drug-specific RASs that are found at a lower frequency may not convey sufficient resistance to reduce SVR with currently available DAA regimens.

Assays

Methods to detect RASs include population sequencing (aka, Sanger sequencing) and deep sequencing (aka, next generation sequencing [NGS]). Both methods depend on sequencing the HCV RNA, calculating the amino acid sequence, and then inferring the presence of RASs. The methods differ in their sensitivity for detecting RASs. For the purposes of clinical care and decisions regarding which DAA regimen to use, both methods can be considered equivalent if a ≥15% cut point is used for determination of RASs by NGS. Recent studies have shown that NGS at a 1% level of sensitivity often result in the identification of additional RASs that are not associated with clinical failure (Jacobson, 2015b); (Sarrazin, 2016); (Zeuzem, 2017).

1. Genotypic Analysis
   a. Population-Based Sequencing (Sanger)
      Population sequencing of the HCV coding region of interest may be performed using reverse transcription polymerase chain reaction (PCR) and standard Sanger sequencing of the bulk PCR product. The sensitivity for detection of resistance substitutions varies but is generally 15% to 25%. As a standard, substitutions are reported as differences compared with a genotype-specific, wild-type strain.

   b. Deep Sequencing Analysis
      NGS (deep sequencing approaches) can increase the sensitivity of detection for minor variants. After sequencing HCV coding regions using PCR, a software algorithm is used to process and align sequencing data via a multistep method to identify the substitutions present at a predetermined level. This level, or threshold, can vary but is often set as low as >1% for research purposes. To approximate results obtained by population sequencing, NGS thresholds are often set to ≥10%.

2. Phenotypic Analysis
   Phenotypic analysis involves laboratory techniques whereby the degree of drug resistance conferred by an amino acid change as well as the replicative capacity (fitness) of a particular RAS can be estimated in the presence of a wild-type or consensus strain. These research techniques are not routinely used for clinical practice. To assess the level of resistance, RASs are typically introduced as point mutations into the backbone of an existing standard HCV genome within an existing cell culture/replicon or enzyme-based assay. Isolates harboring these RASs are then challenged by appropriate antiviral agents at increasing concentrations and fold changes—based on EC_{50} or IC_{50} and EC_{90} or IC_{90} values—are determined for inhibition of replication or enzyme activity, respectively, in comparison to wild-type virus. Comparison of replication levels for variants and wild-type constructs in the absence of drug allows for estimation of fitness.

3. Assay Summary Points

- Either population sequencing or deep sequencing can be used to detect the presence of RASs in NS3, NS5A, and NS5B.
- For clinical decisions, population sequencing or deep sequencing with at least 15% prevalence of RASs as the cutoff is recommended. The presence of RASs with <15% prevalence should not be considered clinically significant.
- When assessing the potential clinical effect of RASs, it is important to determine the drug-specific RASs.

Resistance Testing in Clinical Practice

Regimen-Specific Recommendations for Use of RAS Testing in Clinical Practice

RECOMMENDED	RATING
Elbasvir/grazoprevir NS5A RAS testing is recommended for genotype 1a-infected, treatment-naive or -experienced patients being considered for elbasvir/grazoprevir. If present, weight-based ribavirin should be added and treatment should be extended to 16 weeks, or a different recommended therapy used.	I, A
Ledipasvir/sofosbuvir NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients without cirrhosis being considered for ledipasvir/sofosbuvir. If >100-fold resistance is present, treatment should include 12 weeks of therapy with weight-based ribavirin, or a different recommended therapy.	I, A
NS5A RAS testing can be considered for genotype 1a-infected, treatment-experienced patients with cirrhosis being considered for ledipasvir/sofosbuvir. If >100-fold resistance is present, treatment should include 24 weeks of therapy with weight-based ribavirin, or a different recommended therapy used.	I, A
Sofosbuvir/velpatasvir NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients (with or without cirrhosis) and treatment-naive patients with cirrhosis being considered for 12 weeks of sofosbuvir/velpatasvir. If Y93H is present, weight-based ribavirin should be added.	I, A
Daclatasvir plus sofosbuvir NS5A RAS testing is recommended for genotype 3-infected, treatment-experienced patients without cirrhosis being considered for 12 weeks of daclatasvir plus sofosbuvir. If Y93H is present, weight-based ribavirin should be added.	I, B
NS5A RAS testing is recommended for genotype 3-infected, treatment-naive patients with cirrhosis being considered for 24 weeks of daclatasvir plus sofosbuvir. If Y93H is present, treatment should include weight-based ribavirin, or a different recommended therapy used.	I, B

Regimen-Specific Clinical Practice Situations in Which RAS Testing Is Not Recommended

NOT RECOMMENDED	RATING
Elbasvir/grazoprevir RAS testing is not recommended for any genotype 1b-infected patients being considered for elbasvir/grazoprevir therapy.	I, A
Glecaprevir/pibrentasvir RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for glecaprevir/pibrentasvir for 8, 12, or 16 weeks.	I, A
Ledipasvir/sofosbuvir NS5A RAS testing is not recommended for any genotype 1b-infected patients being considered for ledipasvir/sofosbuvir therapy.	I, A
NS5A RAS testing is not recommended for genotype 1a-infected, treatment-naive patients being considered for ledipasvir/sofosbuvir therapy.	I, A
NS5A RAS testing is not recommended for genotype 1a- or 1b-infected, treatment-naive patients without cirrhosis and with a viral load <6 million IU/mL being considered for an 8-week course of ledipasvir/sofosbuvir therapy.	I, A
Paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin, or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin RAS testing is not recommended for genotype 1- or 4-infected, treatment-naive or -experienced patients being considered for therapy with paritaprevir/ritonavir/ombitasvir with dasabuvir ± weight-based ribavirin or paritaprevir/ritonavir/ombitasvir + weight-based ribavirin, respectively.	I, A
Sofosbuvir/velpatasvir RAS testing is not recommended for patients with genotype 1, 2, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir therapy.	I, A
Sofosbuvir/velpatasvir/voxilaprevir RAS testing is not recommended for patients with genotype 1, 2, 3, 4, 5, or 6 infection being considered for 12 weeks of sofosbuvir/velpatasvir/voxilaprevir therapy.	I, A

Resistance testing is most important in clinical practice when the results would modify treatment management by impacting the duration of therapy and/or inclusion of ribavirin, or result in selection of alternative therapy. Unfortunately, at this time, the utility of RAS testing varies by both patient characteristics and DAA regimen.

Approaches to Overcome Resistance

Data for currently approved DAAs provide limited insight on optimal retreatment approaches for patients with a previous DAA therapy failure and high fold change RASs, particularly those in NS5A. Until regimens combining multiple drugs predicted to be active (based on the available resistance profile) are available and adequate phase 2/3 studies in DAA

treatment failure populations are accomplished, other aspects of therapy must be optimized in treatment-experienced patients with RASs. In general, optimization involves appropriately characterizing the patient along with use of an extended duration of therapy and the addition of ribavirin (unless an absolute contraindication to ribavirin exists).

Characterizing Patients at Risk
The characteristics that increase the risk of DAA treatment failure are different for each oral regimen. Thus, understanding the population at risk is imperative. Generally, this requires accurate assessment of liver fibrosis and clarification of prior therapy.

Virus
Determination of HCV genotype, subtype, and baseline RASs may be necessary to fully characterize a patient's risk for therapeutic failure and optimize the treatment approach.

Treatment Duration
The duration of therapy should always be optimized to attain a cure. Although short-duration therapy has been associated with a higher chance of relapse, careful selection of patients for shortened therapy may minimize relapse risk and lead to significant cost savings. In contrast, extension of therapy (often to 24 weeks) in conjunction with the addition of ribavirin has been associated with reasonable SVR rates during retreatment of patients with past DAA therapy failure, even in the presence of significant drug-specific RASs prior to retreatment (Cooper, 2016); (Gane, 2016).

Ribavirin
The addition of ribavirin increases SVR in patient populations with an increased risk for treatment failure (eg, decompensated cirrhosis). It also improves SVR rates among patients with baseline NS5A RASs and prior DAA treatment failure.

Complementary Therapy
Although data are limited, patients with multiclass RASs can achieve SVR by combining triple or quadruple drug class regimens (see section on retreatment in prior DAA failure). This approach may become less necessary with the approval of standalone dual- or triple-drug regimens composed of second-generation protease and NS5A inhibitors with improved activity against common RASs.

Considerations With Current Antiviral Regimens

Daclatasvir + Sofosbuvir
Daclatasvir plus sofosbuvir is most commonly used for genotype 3-infected individuals. The phase 3 ALLY-3 study had an overall SVR rate of 89% in treatment-naive and -experienced, genotype 3-infected patients treated with 12 weeks of daclatasvir plus sofosbuvir without ribavirin. This study demonstrated that lower SVR rates were observed in patients with cirrhosis, irrespective of treatment experience (97% [73/75] SVR without cirrhosis vs 58% [11/19] SVR with cirrhosis). When RAS impact was assessed, the presence of baseline Y93H was associated with a lower SVR rate in those with cirrhosis. Thirteen patients had Y93H at baseline; 67% (6/9) without cirrhosis achieved SVR whereas only 25% (1/4) with cirrhosis achieved SVR (Nelson, 2015). The subsequent ALLY-3+ study evaluated 12 weeks or 16 weeks of daclatasvir plus sofosbuvir and ribavirin in treatment-naive or -experienced patients with genotype 3 infection and advanced fibrosis or compensated cirrhosis. The overall SVR rate was 90%. Again, virologic failure was higher in individuals with cirrhosis (86% SVR) compared to those with stage 3 fibrosis (100% SVR). Increased treatment duration did not appear to improve efficacy. Eight patients had a baseline RAS, including 2 with Y93H, 5 with A30K, and 1 with A30A/K. The only relapse occurred in a patient with the Y93H RAS (Leroy, 2016).

Elbasvir/Grazoprevir
Elbasvir/grazoprevir is indicated for treatment-naive and -experienced patients with genotype 1 or 4 infection. The presence of NS3 RASs has no significant impact on SVR12 in patients treated with elbasvir/grazoprevir. The presence of NS5A RASs has no significant impact in genotype 1b infection.

In treatment-naive, genotype 1a-infected patients (with or without cirrhosis) treated with 12 weeks of therapy, the

presence of NS3 RASs has no impact (Zeuzem, 2015). In treatment-naive or prior relapse patients treated for 12 weeks with elbasvir/grazoprevir without ribavirin, the presence of high fold change NS5A RASs (at amino acid positions 28, 30, 31, and 93) decreased SVR to 58% (14/24) compared to 98% SVR in those without NS5A RASs. The presence of NS5A RASs had a similar impact on treatment-experienced patients (with or without cirrhosis) who received 12 weeks of elbasvir/grazoprevir without ribavirin (SVR12 29% vs 97%, respectively) (Jacobson, 2015b).

Glecaprevir/Pibrentasvir

In a study of the resistance profiles of glecaprevir and pibrentasvir using cell cultures (Ng, 2017), selection of genotypes 1a, 1b, 2a, 3a, 4a, and 6a replicons for reduced susceptibility to glecaprevir resulted in the emergence of RASs at A156 or D/Q168. The A156 RAS resulted in the greatest reductions (>100-fold) in glecaprevir susceptibility. The D/Q168 RAS had varying effects on glecaprevir susceptibility depending on genotype/subtype and specific amino acid change; the greatest reductions (>30-fold) were observed in genotypes 1a (D168F/Y), 3a (Q168R), and 6a (D168A/G/H/V/Y). However, these RASs are rarely detected clinically. Pibrentasvir selected no viable colonies in genotype 1b, 2b, 4a, 5a, and 6a. Of the few RASs selected by pibrentasvir, Y93H/N conferred <7-fold resistance.

The presence of RAS at baseline had minimal impact on SVR rates with glecaprevir/pibrentasvir in registration trials, that predominantly enrolled non-cirrhotic subjects. In a pooled analysis of NS3/4A protease inhibitor- and NS5A inhibitor-naive patients who received glecaprevir/pibrentasvir in phase 2 and 3 studies (Forns, 2017); (Foster, 2017); (Asselah, 2016); (Zeuzem, 2016); (Kwo, 2017b), baseline RASs in patients with genotype 1, 2, 4, 5, or 6 infection had no impact on SVR12 (Krishnan, 2017). Among treatment-naive genotype 3-infected patients without cirrhosis who received glecaprevir/pibrentasvir for 8 weeks, the A30K polymorphism was detected in 10%, of whom 78% achieved SVR12. There are insufficient data to characterize the impact of A30K in genotype 3-infected patients with cirrhosis or prior treatment experience. All genotype 3-infected patients with Y93H prior to treatment achieved SVR12.

Ledipasvir/Sofosbuvir

Several comprehensive analyses of genotype 1-infected patients treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies have helped clarify the impact of baseline RASs on SVR rates with this regimen (Sarrazin, 2016); (Zeuzem, 2017). In a pooled analysis of patients with genotype 1a or 1b infection who received ledipasvir/sofosbuvir, 93.5% (316/338) of those with baseline NS5A RASs achieved SVR12 compared to an SVR12 rate of 98.4% (1,741/1,770) in patients without baseline NS5A RASs (Sarrazin, 2016). In this analysis, the reduction in SVR rate was driven predominantly by patients with genotype 1a NS5A RASs. The SVR12 rates for genotype 1a-infected patients with and without NS5A RASs were 92.3% and 98.3%, respectively. A slightly lower SVR12 rate of 90% was observed for genotype 1a-infected patients with NS5A RASs using a 15% deep sequencing cutoff value.

Notably, other factors further delineated populations at risk for relapse in this analysis, including high-level baseline NS5A RASs (>100-fold resistance with Q30H/R, L31M/V, and Y93C/H/N in genotype 1a) and a shorter duration therapy (8 weeks or 12 weeks vs 24 weeks). SVR12 rates were 97.4% to 100% in treatment-experienced patients without NS5A RASs or with RASs with <100-fold resistance treated with ledipasvir/sofosbuvir for 12 weeks or 24 weeks. However, when RASs with >100-fold resistance were present, SVR12 rates dropped to 64.7% (11/17) with 12 weeks of therapy compared to 100% (6/6) with 24 weeks of therapy. In this small subset of patients, the addition of ribavirin did not appear to offer the same benefit as extension of therapy to 24 weeks in this pooled analysis. SVR12 rate was 81.8% in those with >100-fold NS5A resistance who received 12 weeks of ledipasvir/sofosbuvir with ribavirin. In contrast, in the SIRIUS trial, all 8 treatment-experienced cirrhotic patients with >100-fold resistance treated for 12 weeks with ledipasvir/sofosbuvir plus ribavirin achieved SVR12.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir ± Ribavirin

Paritaprevir/ritonavir/ombitasvir plus dasabuvir is currently indicated for genotype 1-infected patients. Paritaprevir/ritonavir/ombitasvir is indicated for genotype 4-infected patients, including those with prior peginterferon/ribavirin therapy failure. Patients with genotype 1a or 4 infection receive the addition of ribavirin whereas genotype 1b-infected patients do not. RAS testing has not been demonstrated to impact SVR rates, partially due to the addition of ribavirin in those patients at higher risk for treatment failure in the setting of RASs. Use of *paritaprevir/ritonavir/ombitasvir plus dasabuvir alone in patients with a history of prior DAA treatment failure is not* recommended.

Sofosbuvir/Velpatasvir

Sofosbuvir/velpatasvir is a pangenotypic therapy indicated for treatment-naive and -experienced patients with or without cirrhosis. The presence of NS5A RASs had no impact on SVR12 for patients with genotype 1, 2, 4, 5, or 6 infection treated with sofosbuvir/velpatasvir for 12 weeks in the ASTRAL studies (Hézode, 2016). The presence of Y93H in genotype 3-infected patients decreased the SVR12 rate to 84% (21/25 patients) compared to 97% (242/249) in those without this RAS (Foster, 2015a). This appeared to be more impactful in patients with cirrhosis and/or prior treatment experience with an interferon-based regimen. Ribavirin was not used in these trials and thus, an evidence-based strategy to improve efficacy in those with genotype 3 infection and the NS5A Y93H RAS is not known.

Sofosbuvir/Velpatasvir/Voxilaprevir

Sofosbuvir/velpatasvir/voxilaprevir fills an important role as a pangenotypic regimen for patients who have experienced treatment failure with DAA therapy. The presence of NS3, NS5A, or NS5B RASs prior to treatment did not influence the likelihood of SVR12, and 12 weeks of treatment produced high SVR12 rates (96%) in DAA-experienced patients. RAS testing has not been demonstrated to impact SVR rates with sofosbuvir/velpatasvir/voxilaprevir therapy (Bourlière, 2017).

Table 1. Most Common, Clinically Important RASs by DAA, Genotype, and Fold Change

DAA	Genotype 1a				Genotype 1b	
	M28T	Q30R	L31M/V	Y93H/N	L31V/I	Y93H/N
Ledipasvir	20x	>100x	>100x / >100x	>1000x / >10,000	>100x/ >50x	>100x / --
Ombitasvir	>1000x	>100x	<3x / >100x	>10,000x / >10,000x	<10x	20x / 50x
Daclatasvir	>100x	>1000x	>100x / >1000x	>1000x / >10,000x	<10x	20x / 50x
Elbasvir	20x	>100x	>10x / >100x	>1000x / >1000x	<10x	>100x / --
Velpatasvir	<10x	<3x	20x / 50x	>100x/ >1000x	<3x	<3x / --

Color Key: light green = <3-fold change; dark green = <10-fold change; orange = >10- to 100-fold change; pink = >100-fold change

Table 2. Clinically Important RASs by DAA Regimen and Genotype

DAA Regimen	Genotype		
	1a	1b	3
Ledipasvir/sofosbuvir	Q30H/R L31M/V Y93C/H/N	L31V ?Y93H	n/a
Elbasvir/grazoprevir	M28A/T Q30H/R L31M/V Y93C/H/N	Y93H	n/a
Paritaprevir/ritonavir/ombitasvir with dasabuvir ± ribavirin	n/a	n/a	n/a
Sofosbuvir/velpatasvir	n/a	n/a	Y93H

Table 3. NS5A RAS Testing Recommendations Prior to Initiation of DAA Treatment Among Genotype 1 Patients by DAA Regimen, Virus Subtype, Prior Treatment Experience, and Cirrhosis Status

DAA Regimen	1b TN or TE	1a TN	1a TE No Cirrhosis	1a TE Cirrhosis
Ledipasvir/sofosbuvir	No	No	Yes	Yes
Elbasvir/grazoprevir	No	Yes	Yes	Yes
Sofosbuvir/velpatasvir	No	No	No	No
Paritaprevir/ritonavir/ombitasvir with dasabuvir ± ribavirin	No	No	No	No

[a] TN = treatment naive
[b] TE = treatment experienced

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Initial Treatment of HCV Infection

Initial treatment of HCV infection includes patients with chronic hepatitis C who have not been previously treated with interferon, peginterferon, ribavirin, or any HCV direct-acting antiviral (DAA) agent, whether experimental, investigational, or US Food and Drug Administration (FDA) approved.

The level of evidence available to inform the best regimen for each patient and the strength of the recommendation vary, and are rated accordingly (see Methods Table 2). In addition, specific recommendations are given when treatment differs for a particular group (eg, those infected with different genotypes). Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and treatment duration. Alternative regimens are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. In certain situations, an alternative regimen may be an optimal regimen for an individual patient. Not recommended regimens are clearly inferior compared to recommended or alternative regimens based on factors such as lower efficacy, unfavorable tolerability and toxicity, longer treatment duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection. Specific considerations for pediatric patients and persons with HIV/HCV coinfection, decompensated cirrhosis (moderate or severe hepatic impairment; Child-Turcotte-Pugh [CTP] class B or C), HCV infection post liver transplant, and severe renal impairment, end-stage renal disease (ESRD), or post kidney transplant are addressed in other sections of the guidance.

Simplification of the treatment regimen may expand the number of healthcare professionals who prescribe antiviral therapy and increase the number of persons treated. This would align with the National Academies of Science, Engineering, and Medicine strategy to reduce cases of chronic HCV infection by 90% by 2030 (NASEM, 2017).

Recommended and alternative regimens are listed in order of level of evidence. When several regimens are at the same recommendation level, they are listed in alphabetical order. Regimen choice should be determined based on patient-specific data, including drug-drug interactions. Patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients require careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen (see Monitoring section).

The following pages include guidance for management of treatment-naive patients.

- Genotype 1
- Genotype 2
- Genotype 3
- Genotype 4
- Genotype 5 or 6

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with DAAs are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration of treatment is unclear, expert consultation should be sought.

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Treatment-Naive Genotype 1

Four highly potent DAA combination regimens are recommended for patients with genotype 1 infection, although there are differences in the recommended regimens based on the HCV subtype, the presence or absence of baseline NS5A resistance-associated substitutions (RASs), and the presence or absence of compensated cirrhosis.

With certain regimens, patients with genotype 1a may have higher virologic failure rates than those with genotype 1b. Genotype 1 infection that cannot be subtyped should be treated as genotype 1a infection.

Approximately 10% to 15% of genotype 1-infected patients without prior exposure to NS5A inhibitors have detectable NS5A RASs prior to treatment. The clinical impact of NS5A RASs varies across regimens and baseline patient characteristics. In patients with genotype 1a infection, the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (>5 fold) adversely impacts response to some NS5A inhibitor-containing regimens (Zeuzem, 2017); (Jacobson, 2015b). These RASs are found by population sequencing in roughly 5% to 10% of patients and relevant RASs vary by DAA regimen. Given that baseline NS5A RASs are one of the strongest pretreatment predictors of therapeutic response with certain regimens in those with genotype 1a infection, testing for these RASs prior to deciding on a therapeutic course is recommended in select situations (Zeuzem, 2015c). For further guidance, please see the HCV Resistance Primer section.

Compared to interferon-based therapy, DAAs are associated with an increased risk of drug-drug interactions with concomitant medications. Thus, attention to drug interactions is an important treatment consideration (see Drug Interactions table). The product prescribing information and other resources (eg, http://www.hep-druginteractions.org) should be referenced regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all the regimens discussed.

The following pages include guidance for management of treatment-naive patients with genotype 1 infection.

- Treatment-Naive Genotype 1a Without Cirrhosis
- Treatment-Naive Genotype 1b Without Cirrhosis
- Treatment-Naive Genotype 1a With Compensated Cirrhosis
- Treatment-Naive Genotype 1b With Compensated Cirrhosis

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Treatment-Naive Genotype 1a Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:
Treatment-Naive Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[a] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), with weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs[a] for elbasvir	16 weeks	IIa, B

[a] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

For genotype 1a-infected, treatment-naive patients without cirrhosis, there are 4 recommended regimens with comparable efficacy. Four regimens are classified as alternative because, compared to the recommended regimens, they require a longer duration of treatment, involve greater prescribing complexity, are potentially less efficacious, and/or there are limited supporting data.

Recommended Regimens

Elbasvir/Grazoprevir

The fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) is recommended based on data from the phase 3 C-EDGE trial, which assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) (Zeuzem, 2015f). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred eighty-two patients (91% of the study cohort) were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The sustained virologic response rates at 12 weeks (SVR12) were 92% (144/157) in treatment-naive patients with genotype 1a infection and 99% (129/131) in genotype 1b patients. Findings from this phase 3 study support earlier phase 2 findings from the C-WORTHY trial in which SVR12 rates of 92% (48/52) and 95% (21/22) were demonstrated among genotype 1a and genotype 1b treatment-naive, noncirrhotic patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin (Sulkowski, 2015b). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients.

The presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of elbasvir/grazoprevir in genotype 1a-infected patients (Zeuzem, 2017). Baseline NS5A RASs were identified in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study, of which 58% (11/19) achieved SVR12 compared to an SVR12 rate of 99% (133/135) in patients without these RASs receiving 12 weeks of elbasvir/grazoprevir (Zeuzem, 2017). Among treatment-naive patients, the presence of baseline NS5A RASs with greater than 5-fold reduced sensitivity to elbasvir was associated with the most significant reduction in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12.

Recommendations for prolonging treatment duration to 16 weeks with inclusion of ribavirin for treatment-naive genotype 1a patients with baseline NS5A RASs is based on extrapolation of data from the C-EDGE TE trial. In this phase 3 open-label trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, among 58 genotype 1a-infected patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures (Kwo, 2017). Subsequent integrated analysis of the elbasvir/grazoprevir phase 2 and 3 trials demonstrated an SVR12 rate of 100% (6/6) in genotype 1 patients with pretreatment NS5A RASs treated with elbasvir/grazoprevir plus ribavirin for 16 or 18 weeks (Jacobson, 2015b); (Thompson, 2015).

Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for elbasvir/grazoprevir therapy. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Glecaprevir/Pibrentasvir

The daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) is administered as three 100 mg/40 mg fixed-dose combination pills. Based on favorable data for 8 weeks of treatment among noncirrhotic patients in the phase 2 SURVEYOR-1 study (33/34 patients with SVR and no virologic failures) (Kwo, 2017b), ENDURANCE-1 enrolled 703 *noncirrhotic, genotype 1 patients who were DAA-naive or in whom a previous interferon-based regimen failed. Participants* were randomized to receive 8 or 12 weeks of glecaprevir/pibrentasvir (Zeuzem, 2016). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage 0 or 1, and 62% were treatment naive. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority to the 12-week arm. A single patient experienced on-treatment virologic failure in this study (genotype 1a, day 29). Notably, there were no documented relapses in either study arm.

EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12. The single relapse

occurred in a genotype 1a patient; SVR for genotype 1a was 98% (47/48) (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection (Rockstroh, 2017). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on a pair of registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 was 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

ION-3 excluded patients with cirrhosis and investigated shortening therapy from 12 weeks to 8 weeks (with or without ribavirin) (Kowdley, 2014). SVR12 rates were 93% to 95% across all study arms with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20/431)—regardless of ribavirin use—compared with the 12-week arm (3/216). Post hoc analyses of the ribavirin-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients receiving 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels <6 million IU/mL (2/123; 2%). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2/131; 2%). This analysis was not controlled, which limits the generalizability of this approach to clinical practice.

Published, real-world cohort data generally show comparable effectiveness of 8-week and 12-week courses of ledipasvir/sofosbuvir in treatment-naive patients without cirrhosis (Backus, 2016); (Ingiliz, 2016); (Ioannou, 2016); (Kowdley, 2016); (Terrault, 2016). However, only about half of patients eligible for 8 weeks of treatment received it, assignment of duration was not randomized, and baseline characteristics may have varied between 8- and 12-week groups.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV/HCV-coinfected patients (see HIV/HCV Coinfection section) and black patients (Su, 2016); (Wilder, 2016); (O'Brien, 2014); (Ioannou, 2016). For others, it should be done at the discretion of the practitioner with consideration of other potential negative prognostic factors.

Sofosbuvir/Velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201) (Feld, 2015). Of the 328 genotype 1 patients included, 323 achieved SVR with no difference observed by subtype (98% 1a; 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR rate for genotype 1 (Hézode, 2016). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotypes 1, 2, 3, 4, 5, or 6—with or without compensated cirrhosis—to receive 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir (Jacobson, 2017). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with

genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed with each subtype.

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir and Ribavirin

The daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) and weight-based ribavirin was approved by the FDA for the treatment of genotype 1a infection in treatment-naive patients based on 3 registration trials: SAPPHIRE-I (322 treatment-naive patients with genotype 1a infection without cirrhosis); PEARL-IV (305 treatment-naive patients with genotype 1a without cirrhosis); and TURQUOISE-II (261 treatment-naive and -experienced patients with genotype 1a and cirrhosis).

The SAPPHIRE-I trial reported a 95.3% SVR12 rate with 12 weeks of paritaprevir/ritonavir/ombitasvir + dasabuvir and ribavirin (Feld, 2014). Overall, virologic failure was higher for patients with genotype 1a (7/8 failures) than genotype 1b (1/8 failures). PEARL-IV was specifically designed to determine the role of paritaprevir/ritonavir/ombitasvir + dasabuvir—with or without weight-based ribavirin—for treatment-naive, genotype 1a-infected patients without cirrhosis (Ferenci, 2014).

SVR12 was lower in the ribavirin-free arm than in the ribavirin-containing arm (90% vs 97%, respectively) due to higher rates of virologic failure (7.8% vs 2%, respectively), confirming the need for weight-based ribavirin for patients with genotype 1a. An extended-release formulation of paritaprevir/ritonavir/ombitasvir + dasabuvir was approved in 2016, allowing once-daily dosing; ribavirin, when needed, remains at twice-daily dosing (AbbVie Inc, 2017).

Simeprevir + Sofosbuvir

The OPTIMIST-1 trial investigated the safety and efficacy of simeprevir (150 mg) and sofosbuvir (400 mg) in patients with genotype 1 without cirrhosis. In this study, 310 treatment-naive and -experienced patients without cirrhosis were randomly assigned to 12 or 8 weeks of the simeprevir plus sofosbuvir regimen (Kwo, 2016). Overall SVR12 rates were 97% (150/155) for the 12-week arm and 83% (128/155) for the 8-week arm, with a statistically significantly greater relapse rate in the 8-week arm. In the 12-week arm, there was no difference in SVR12 based on past treatment experience; treatment-naive and -experienced patients achieved SVR12 rates of 97% and 95%, respectively. There was also no difference in SVR12 based on genotype 1 subtype or the presence of the baseline Q80K resistance substitution.

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for the treatment of genotype 1 infection is recommended based on data from the phase 3 ALLY-2 trial, which assessed the efficacy and safety of daclatasvir and sofosbuvir for 12 weeks in patients coinfected with HIV and HCV (genotype 1, 2, 3, or 4) (Wyles, 2015). One hundred twenty-three (83%) patients receiving 12 weeks of therapy in the trial were infected with genotype 1. Eighty-three (54%) of these patients were treatment naive. The SVR rate was 96% in treatment-naive patients with genotype 1a infection (n=71) receiving 12 weeks of therapy. Similarly, in a phase 2b study of daclatasvir plus sofosbuvir among 88 treatment-naive patients with genotype 1a infection—21 treated for 24 weeks (11 with ribavirin) and 67 treated for 12 weeks (33 with ribavirin)—there were no virologic relapses (Sulkowski, 2014a).

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Treatment-Naive Genotype 1a With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for Treatment-Naive Genotype 1a Patients With Compensated Cirrhosis[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with weight-based ribavirin for patients with baseline NS5A RASs[b] for elbasvir	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

For genotype 1a-infected, treatment-naive patients with compensated cirrhosis, there are 4 recommended regimens with comparable efficacy. The alternative regimen is classified as such because, compared to the recommended regimens, it requires a longer duration of treatment, involves greater prescribing complexity, is potentially less efficacious, and/or there are limited supporting data.

Recommended Regimens

Elbasvir/Grazoprevir

The recommendation for use of daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) in cirrhotic patients with genotype 1 infection is based on 92 patients (22% of the study cohort) in the phase 3 C-EDGE trial who had Metavir F4 disease (Zeuzem, 2015f). SVR12 was 97% in this subgroup of cirrhotic patients. A similar 97% (28/29) SVR12 rate had previously been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients (Lawitz, 2015c). Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen (Lawitz, 2015c); (Zeuzem, 2017).

Presence of certain baseline NS5A RASs significantly reduces SVR12 rates with a 12-week course of the elbasvir/grazoprevir regimen in genotype 1a-infected patients (Zeuzem, 2017). Baseline NS5A RASs were identified in 12% (19/154) of genotype 1a-infected patients enrolled in the C-EDGE study, of which 58% (11/19) achieved SVR12 compared to 99% (133/135) in patients without these RASs (Zeuzem, 2017). Among treatment-naive patients, the

presence of baseline NS5A RASs with a greater than 5-fold reduced sensitivity to elbasvir was associated with the most significant reduction in SVR12 with only 22% (2/9) of genotype 1a patients with these RASs achieving SVR12.

Recommendations for prolonging duration of treatment to 16 weeks with inclusion of ribavirin for treatment-naive genotype 1a patients with baseline NS5A RASs is based on extrapolation of data from the C-EDGE TE trial. In this phase 3 open-label trial of elbasvir/grazoprevir that enrolled treatment-experienced patients, among 58 genotype 1a patients who received 16 weeks of therapy with elbasvir/grazoprevir plus ribavirin, there were no virologic failures (Kwo, 2017). Subsequent integrated analysis of elbasvir/grazoprevir phase 2 and 3 trials demonstrated an SVR12 rate of 100% (6/6 patients) in genotype 1 patients with pretreatment NS5A RASs treated with elbasvir/grazoprevir for 16 or 18 weeks plus ribavirin (Jacobson, 2015b); (Thompson, 2015).

Based on known inferior response in patients with baseline NS5A RASs, NS5A resistance testing is recommended in genotype 1a patients who are being considered for elbasvir/grazoprevir therapy. If baseline RASs are present (ie, substitutions at amino acid positions 28, 30, 31, or 93), treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Glecaprevir/Pibrentasvir

EXPEDITION-1 investigated the use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12. The single relapse occurred in a genotype 1a patient; SVR among these patients was 98% (47/48) (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection (Rockstroh, 2017). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on 2 registration trials: ION-1 (865 treatment-naive patients; those *with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded).* ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 rates were 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

Sofosbuvir/Velpatasvir

The daily fixed-dose combination sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment-naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201) (Feld, 2015). Of the 328 genotype 1 patients included, 323 achieved SVR with no difference in SVR observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR rate for genotype 1 (Hézode, 2016). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotype 1, 2, 3, 4, 5, or 6—19% with cirrhosis—to receive 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir (Jacobson, 2017). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed with each subtype.

Last update: September 21, 2017

Treatment-Naive Genotype 1b Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Patients Genotype 1b Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) for patients who are non-black, HIV-uninfected, and whose HCV RNA level is <6 million IU/mL	8 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	12 weeks	I, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

For genotype 1b-infected, treatment-naive patients without cirrhosis, there are 4 regimens of comparable efficacy. Three additional regimens are classified as alternative because, compared to the recommended regimens, they require a longer duration of treatment, involve greater prescribing complexity, are potentially less efficacious, and/or there are limited supporting data.

Recommended Regimens

Elbasvir/Grazoprevir

The fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) is recommended based on data from the phase 3 C-EDGE trial, which assessed the efficacy and safety of this regimen for 12 weeks in treatment-naive adults (genotypes 1, 4, and 6) (Zeuzem, 2015f). Patients were enrolled from 60 centers in 9 countries on 4 continents. Three hundred eighty-two patients (91% of the study cohort) were infected with genotype 1 (50% genotype 1a, 41% genotype 1b). The SVR12 was

92% (144/157) in treatment-naive patients with genotype 1a and 99% (129/131) in those with genotype 1b. Findings from this phase 3 study support earlier phase 2 findings from the C-WORTHY trial in which SVR12 rates of 92% (48/52) and 95% (21/22) were demonstrated among genotype 1a and genotype 1b treatment-naive noncirrhotic patients, respectively, who received 12 weeks of elbasvir/grazoprevir without ribavirin (Sulkowski, 2015b). The C-WORTHY trial enrolled both HCV-monoinfected and HIV/HCV-coinfected patients.

In contrast to genotype 1a, the presence of baseline substitutions associated with NS5A resistance did not appear to affect genotype 1b response to elbasvir/grazoprevir. Thus, current data do not support extending the treatment duration or adding ribavirin in genotype 1b patients with NS5A RASs.

Glecaprevir/Pibrentasvir

Based on favorable data for 8 weeks of treatment for noncirrhotic patients in the phase 2 SURVEYOR-1 study (33/34 patients with SVR and no virologic failures) (Kwo, 2017b), ENDURANCE-1 enrolled 703 noncirrhotic, genotype 1 patients who were DAA-naive or in whom a previous interferon-based regimen failed. Participants were randomized to receive 8 weeks or 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills (Zeuzem, 2016). Of those enrolled, 43% had genotype 1a, 85% had fibrosis stage 0 or 1, and 62% were treatment naive. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority to the 12-week arm. A single patient experienced on-treatment virologic failure in this study (genotype 1a, day 29). Notably, there were no documented relapses in either arm.

EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12. All genotype 1b patients achieved SVR (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected persons with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection (Rockstroh, 2017). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

Ledipasvir/Sofosbuvir

The fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on a pair of registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 rates were 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

ION-3 excluded patients with cirrhosis and investigated shortening ledipasvir/sofosbuvir therapy from 12 weeks to 8 weeks (with or without ribavirin) (Kowdley, 2014). SVR12 rates were 93% to 95% across all study arms, with no difference in SVR in the intention-to-treat analysis. However, relapse rates were higher in the 8-week arms (20/431)—regardless of ribavirin use—compared with the 12-week arm (3/216). Post hoc analyses of the ribavirin-free arms assessed baseline predictors of relapse and identified lower relapse rates in patients receiving 8 weeks of ledipasvir/sofosbuvir who had baseline HCV RNA levels <6 million IU/mL (2/123; 2%). The same held true for patients with similar baseline HCV RNA levels who received 12 weeks of treatment (2/131; 2%). This analysis was not controlled, which limits the generalizability of this approach to clinical practice.

Published, real-world cohort data generally show comparable effectiveness of 8 and 12 weeks of ledipasvir/sofosbuvir in treatment-naive patients without cirrhosis (Backus, 2016); (Ingiliz, 2016); (Ioannou, 2016); (Kowdley, 2016); (Terrault,

2016). However, only about half of patients eligible for 8 weeks received it, assignment of duration was not randomized, and baseline characteristics may have varied between 8- and 12-week groups.

Based on available data, shortening treatment to less than 12 weeks is not recommended for HIV-infected patients (see HIV/HCV Coinfection section) and black patients (Su, 2016); (Wilder, 2016); (O'Brien, 2014); (Ioannou, 2016). For others, it should be done at the discretion of the practitioner with consideration of other potential negative prognostic factors.

Sofosbuvir/Velpatasvir

The fixed-dose combination of 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment-naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201); (Feld, 2015). Of the 328 genotype 1 patients included, 323 achieved SVR with no difference observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). The presence of baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR rate for genotype 1 (Hézode, 2016). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotypes 1, 2, 3, 4, 5, or 6—with or without compensated cirrhosis—to receive either 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir (Jacobson, 2017). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed in each subtype.

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) was approved by the FDA for the treatment of genotype 1b infection in treatment-naive patients based on 3 registration trials; 2 focused specifically on those without cirrhosis. SAPPHIRE-I, which included 151 treatment-naive, genotype 1b-infected patients without cirrhosis, reported an SVR12 rate of 98% with 12 weeks of paritaprevir/ritonavir/ombitasvir + dasabuvir in these patients (Feld, 2014).

Given the high SVR12 rates seen in SAPPHIRE-I, PEARL-III was specifically designed to determine the role of weight-based ribavirin with paritaprevir/ritonavir/ombitasvir + dasabuvir in treatment-naive, genotype 1b-infected patients without cirrhosis (Ferenci, 2014). The SVR12 rate among the 419 study participants was 99% in both treatment arms, confirming there is no added benefit from use of weight-based ribavirin for patients without cirrhosis who have genotype 1b infection.

GARNET, a phase 3b single-arm study of 163 genotype 1b patients without cirrhosis, demonstrated a 98% SVR rate with an 8-week course of paritaprevir/ritonavir/ombitasvir + dasabuvir. When considering the generalizability of these results, it is important to note that 91% of the GARNET participants had fibrosis stage 0 to 2, 93% had HCV RNA levels <6 million IU/mL, and 96% were white. In addition, 2 of the 15 patients with fibrosis stage 3 experienced virologic relapse, suggesting that if used, an 8-week strategy should be reserved for those with early-stage fibrosis (Welzel, 2016b).

Simeprevir + Sofosbuvir

The OPTIMIST-1 trial investigated the safety and efficacy of simeprevir (150 mg) plus sofosbuvir (400 mg) in patients with genotype 1 without cirrhosis. In this study, 310 treatment-naive and -experienced patients without cirrhosis were randomly assigned to 12 weeks or 8 weeks of the simeprevir plus sofosbuvir regimen (Kwo, 2016). Overall SVR12 rates were 97% (150/155) in the 12-week arm and 83% (128/155) in the 8-week arm, with a statistically significantly greater relapse rate in the 8-week arm. In the 12-week arm, there was no difference in SVR12 based on past treatment experience; treatment-naive and -experienced patients achieved SVR12 rates of 97% and 95%, respectively. There was also no difference in SVR12 based on genotype 1 subtype or the presence of the baseline Q80K resistance substitution.

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for the treatment of genotype 1 infection is recommended based on data from the phase 3 ALLY-2 trial, which assessed the efficacy and safety of daclatasvir/sofosbuvir for 12 weeks in patients coinfected with HIV and HCV (genotype 1, 2, 3, or 4) (Wyles, 2015). One hundred twenty-three (83%) patients receiving 12 weeks of therapy in the trial were infected with genotype 1. Eighty-three (54%) of these patients were treatment naive. Only 12 had genotype 1b and all achieved SVR12 (Wyles, 2015). Furthermore, in the ALLY-1 study, all 11 genotype 1b-infected patients with advanced cirrhosis achieved SVR12. Due to the limited numbers of genotype 1b patients represented in the phase 3 trials of this regimen, there is not enough evidence to support a different approach by subtype at this time.

Last update: September 21, 2017

Treatment-Naive Genotype 1b With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: **Treatment-Naive Genotype 1b Patients With Compensated Cirrhosis**[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)[c]	12 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Please see statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

For genotype 1b-infected, treatment-naive patients with compensated cirrhosis, there are 4 recommended regimens with comparable efficacy. The alternative regimen is classified as such because, compared to the recommended regimens, it requires a longer duration of treatment, involves greater prescribing complexity, is potentially less efficacious, and/or there are limited supporting data.

Recommended Regimens

Elbasvir/Grazoprevir

The recommendation for use of daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) in cirrhotic patients with genotype 1 infection is based on 92 patients (22% of the study cohort) in the phase 3 C-EDGE trial who had Metavir F4 disease (Zeuzem, 2015f). SVR12 was 97% in the subgroup of cirrhotic patients. A similar 97% (28/29) SVR12 rate had previously been demonstrated in genotype 1 cirrhotic treatment-naive patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin in the open-label phase 2 C-WORTHY trial, which enrolled both HCV-monoinfected and HIV/HCV-coinfected patients (Lawitz, 2015c). Presence or absence of cirrhosis does not appear to alter the efficacy of the elbasvir/grazoprevir regimen (Lawitz, 2015c); (Zeuzem, 2017).

Glecaprevir/Pibrentasvir

EXPEDITION-1 investigated use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in DAA-naive (75%) or -experienced (interferon or

peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 145 (99%) achieved SVR12; all genotype 1b patients achieved SVR (Forns, 2017).

EXPEDITION-2, a study of glecaprevir/pibrentasvir in 153 HIV/HCV-coinfected adults with genotype 1, 2, 3, 4, 5, or 6, utilized 8 weeks of treatment for noncirrhotic patients and 12 weeks for cirrhotic patients (the recommended durations approved by the FDA). The overall SVR12 rate was 98% and there were no observed virologic failures among the 94 patients with genotype 1 infection (Rockstroh, 2017). In EXPEDITION-1 and EXPEDITION-2, neither subtype (1a vs 1b) nor the presence of baseline RASs impacted SVR12 results in DAA-naive genotype 1 patients.

Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on 2 registration trials: ION-1 (865 treatment-naive patients; those with cirrhosis were included) and ION-3 (647 treatment-naive patients; those with cirrhosis were excluded). ION-1 investigated length of treatment (12 weeks vs 24 weeks) and the need for ribavirin (Afdhal, 2014a). SVR12 rates were 97% to 99% across all study arms with no difference in SVR based on length of treatment, use of ribavirin, or genotype 1 subtype. Sixteen percent of participants enrolled were classified as having cirrhosis. There was no difference in SVR12 rate in those with cirrhosis (97%) versus those without cirrhosis (98%).

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 1 infection in treatment-naive patients based on ASTRAL-1. This placebo-controlled trial involved a 12-week course of sofosbuvir/velpatasvir administered to 624 participants with genotype 1, 2, 4, 5, or 6 who were treatment-naive (n=423) or previously treated with interferon-based therapy, with or without ribavirin or a protease inhibitor (n=201); (Feld, 2015). Of the 328 genotype 1 patients included, 323 achieved SVR with no difference in SVR observed by subtype (98% 1a, 99% 1b). Of 121 participants (all genotypes) classified as having cirrhosis, 120 achieved SVR (99%). Baseline NS5A RASs (at 15% cutoff)—reported in 11% of genotype 1a and 18% of genotype 1b participant samples tested—did not influence SVR rate for genotype 1 (Hézode, 2016). Of the 2 virologic failures in ASTRAL-1 (<1% of treated participants), both were genotype 1 and had baseline RASs. There was no significant difference in the rates of adverse events in the sofosbuvir/velpatasvir vs placebo groups.

The phase 3 POLARIS-2 study randomized 941 DAA-naive patients with genotypes 1, 2, 3, 4, 5, or 6—19% with compensated cirrhosis—to receive either 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) or 12 weeks of sofosbuvir/velpatasvir (Jacobson, 2017). Of participants treated with sofosbuvir/velpatasvir, 170/172 (99%) with genotype 1a and 57/59 (97%) with genotype 1b achieved SVR with a single relapse observed with each subtype.

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) was approved by the FDA for the treatment of genotype 1b infection in treatment-naive patients based on 3 registration trials: SAPPHIRE-I (151 treatment-naive patients with genotype 1b without cirrhosis); PEARL-III (419 treatment-naive patients with genotype 1b without cirrhosis); and TURQUOISE-II (119 treatment-naive and -experienced patients with genotype 1b and cirrhosis). TURQUOISE-II enrolled treatment-naive and -experienced patients with Child-Turcotte-Pugh class A cirrhosis to receive either 12 weeks or 24 weeks of paritaprevir/ritonavir/ombitasvir + dasabuvir and ribavirin. Overall SVR12 rates were 98.5% in the 12-week arm and 100% in the 24-week arm (Poordad, 2014).

To address the need for ribavirin with this regimen in patients with genotype 1b and cirrhosis, the TURQUOISE-III study evaluated the safety and efficacy of paritaprevir/ritonavir/ombitasvir + dasabuvir without ribavirin for 12 weeks in patients

with genotype 1b infection and compensated cirrhosis. Sixty patients (62% men; 55% treatment-experienced; 83% with the IL28B non-CC genotype; 22% with platelet counts <90 x 10^9/L; 17% with albumin <3.5 g/dL) were enrolled. All patients completed treatment and all achieved SVR12. Based on this study, treating patients with genotype 1b with paritaprevir/ritonavir/ombitasvir + dasabuvir without ribavirin is recommended, regardless of prior treatment experience or the presence of compensated cirrhosis (Feld, 2016).

Last update: September 21, 2017

Treatment-Naive Genotype 2

The following pages include guidance for management of treatment-naive patients with genotype 2 infection.

Last update: September 21, 2017

Treatment-Naive Genotype 2 Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 2 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	12 weeks	IIa, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Glecaprevir/Pibrentasvir

ENDURANCE-2 was a randomized, double-blind, placebo-controlled trial of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks among 302 genotype 2-infected treatment-naive or -experienced participants. Treatment-experienced patients included those previously treated with interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon. Patients randomized to placebo later received open-label treatment with glecaprevir/pibrentasvir for 12 weeks. Among 202 patients randomized to active treatment, 70% (141/202) were treatment naive and none had cirrhosis. The SVR12 rates were 99% and 100% by intention-to-treat and modified intention-to-treat analysis, respectively. There were no virologic failures. One participant who achieved SVR4 was lost to follow-up before the SVR12 evaluation. There was no effect of baseline RASs on SVR12 rate. Overall, therapy was well tolerated and the adverse event profile was not different compared to placebo (Kowdley, 2016b).

A shorter duration of glecaprevir/pibrentasvir for 8 weeks was evaluated in the SURVEYOR-II, part 4 study. This was a single-arm, phase 2 study that evaluated glecaprevir/pibrentasvir for 8 weeks among 203 treatment-naive or -experienced patients (previously treated with interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 2, 4, 5, or 6 infection without cirrhosis. Of the 142 genotype 2-infected patients, 137 (96%) were treatment naive. Among the treatment-naive, genotype 2-infected participants, 135/137 (99%) achieved SVR12. The presence of baseline RASs had minimal effect on SVR12 rates. Fifty-three of 126 (42%) treatment-naive and -experienced participants with genotype 2 had the L31M RAS within the NS5A gene at baseline. Fifty-one of 53 (96%) of these participants achieved SVR12 (Hassanein, 2016).

While not a head-to-head comparison, the results of ENDURANCE-2 and SURVEYOR-II, part 4 indicate that glecaprevir/pibrentasvir administered for 8 or 12 weeks is highly efficacious among genotype 2-infected, treatment-naive patients without cirrhosis.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 2 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-2 compared 12 weeks of sofosbuvir/velpatasvir to 12 weeks of sofosbuvir plus ribavirin in 266 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis. The study showed superior efficacy of sofosbuvir/velpatasvir (SVR12 99% vs 94%); (Foster, 2015a). ASTRAL-1 also included 104 genotype 2 treatment-naive and -experienced participants without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (Feld, 2015). Pooled analysis of all genotype 2 patients in ASTRAL-1 and ASTRAL-2 demonstrated 100% SVR12 in participants with compensated cirrhosis (29/29) and 99% SVR12 in treatment-naive participants (194/195). Among patients with genotype 2 receiving sofosbuvir/velpatasvir, the presence of baseline NS5A or NS5B RASs was not associated with virologic failure.

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three patients with genotype 2 were included in the sofosbuvir/velpatasvir arm and all achieved SVR12 (100%). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection (Jacobson, 2017).

Alternative Regimen

Daclatasvir + Sofosbuvir

A 12-week course of daclatasvir (60 mg) plus sofosbuvir (400 mg) was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. Although this regimen was not approved for the treatment of genotype 2 infection, daclatasvir maintains adequate activity against genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir plus sofosbuvir was associated with high SVR rates in treatment-naive patients with genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014a). It is unclear if there is a subgroup of genotype 2-infected patients who would benefit from extending treatment. For patients who require treatment but cannot tolerate sofosbuvir/velpatasvir or glecaprevir/pibrentasvir, a regimen of daclatasvir plus sofosbuvir for 12 weeks is reasonable.

Last update: September 21, 2017

Treatment-Naive Genotype 2 With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: Treatment-Naive Genotype 2 Patients With Compensated Cirrhosis[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)[b]	12 weeks	I, B
ALTERNATIVE	DURATION	RATING
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	16 to 24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 2 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-2 compared 12 weeks of sofosbuvir/velpatasvir to 12 weeks of sofosbuvir plus ribavirin in 266 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis. The study showed superior efficacy of sofosbuvir/velpatasvir compared to sofosbuvir plus ribavirin (SVR12 99% vs 94%); (Foster, 2015a). ASTRAL-1 also included 104 genotype 2 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (Feld, 2015). Pooled analysis of all genotype 2 patients in ASTRAL-1 and ASTRAL-2 demonstrated 100% SVR12 in those with compensated cirrhosis (29/29) and 99% SVR12 in treatment-naive participants (194/195). Among patients with genotype 2 receiving sofosbuvir/velpatasvir, the presence of baseline NS5A or NS5B RASs was not associated with virologic failure.

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three patients with genotype 2 were included in the sofosbuvir/velpatasvir arm and all achieved SVR12 (100%). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection (Jacobson, 2017).

Glecaprevir/Pibrentasvir

EXPEDITION-1 was a multicenter, open-label, single-arm, phase 3 trial that enrolled 146 treatment-naive or -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 1, 2, 4, 5, or 6

infection and compensated cirrhosis. Participants were treated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks. Across all genotypes, 145/146 (99%) achieved SVR12 (Forns, 2017). EXPEDITION-1 included 31 treatment-naive and -experienced persons with genotype 2 infection and compensated cirrhosis; all achieved SVR12. Baseline NS5A RASs were detected (by next-generation sequencing using a 15% detection cutoff) in 40% of 133 tested participants. Baseline NS5A RASs had no effect on SVR rates among treatment-naive and -experienced patients with genotype 2 infection.

Alternative Regimen

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. Although this regimen was not approved for the treatment of genotype 2 infection, daclatasvir maintains adequate activity against genotype 2 despite a 50% effective concentration (EC_{50}) that increases by several logs in the presence of the prevalent M31 substitution (Wang, 2014). In fact, daclatasvir with sofosbuvir was associated with high SVR rates in treatment-naive patients with genotype 2 infection with both 12 weeks and 24 weeks of therapy (Wyles, 2015); (Sulkowski, 2014a). It is unclear if there is a subgroup of genotype 2-infected patients who would benefit from extending treatment. For patients who require treatment but cannot tolerate sofosbuvir/velpatasvir or glecaprevir/pibrentasvir, a regimen of daclatasvir with sofosbuvir for 12 weeks is reasonable.

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Treatment-Naive Genotype 3

The following pages include guidance for management of treatment-naive patients with genotype 3 infection.

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Treatment-Naive Genotype 3 Without Cirrhosis

Recommended and alternative regimens listed alphabetically for Treatment-Naive Genotype 3 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	12 weeks	I, A

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Glecaprevir/Pibrentasvir

ENDURANCE-3 was a randomized (2:1) trial comparing 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg), administered as three 100 mg/40 mg fixed-dose combination pills, to 12 weeks of sofosbuvir (400 mg) and daclatasvir (60 mg) among 348 treatment-naive participants with genotype 3 infection without cirrhosis. The trial was later amended to include an open-label arm that evaluated glecaprevir/pibrentasvir for an 8-week duration among 157 treatment-naive participants with genotype 3 infection without cirrhosis. Participants receiving glecaprevir/pibrentasvir for 8 or 12 weeks achieved an SVR12 rate of 95% in an intention-to-treat analysis (222/233 participants receiving the 12-week regimen; 149/157 participants receiving the 8-week regimen) (Foster, 2017). Virologic failure was observed in 6 participants receiving the 8-week regimen (1 virologic breakthrough; 5 relapses) and in 4 participants in the 12-week arm (1 virologic breakthrough; 3 relapses). Both the 8- and 12-week glecaprevir/pibrentasvir regimens met noninferiority criteria for SVR12 compared to the standard of care arm of sofosbuvir/daclatasvir, which reported an SVR12 rate of 97%. While the baseline presence of the Y93H substitution did not affect SVR rates (10/10 with Y93H achieved SVR with an 8 week duration vs 165/171 without Y93H), the presence of the A30K substitution was associated with a lower SVR rate (14/18 with A30K achieved SVR with an 8 week duration vs 161/163 without A30K) (Krishnan, 2017). Of the 14 treatment-naive patients with genotype 3 without cirrhosis with baseline A30K who received a 12 week duration of glecaprevir/pibrentavir, 13/14 achieved SVR. Given the small numbers, there is insufficient evidence to recommend testing for RASs or extension of therapy in the setting of A30K at this time, but the effect of the A30K mutation should continue to be explored in real world cohorts. These data support an 8-week regimen of glecaprevir/pibrentasvir for the treatment of genotype 3-infected patients who are treatment-naive without cirrhosis.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for

the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 demonstrated superiority of 12 weeks of sofosbuvir/velpatasvir to 24 weeks sofosbuvir plus ribavirin in 552 treatment-naive and -experienced patients without cirrhosis or with compensated cirrhosis (Foster, 2015a). Among treatment-naive, noncirrhotic patients, SVR12 rates were 98% (160/163) for sofosbuvir/velpatasvir compared to 90% (141/156) for sofosbuvir plus ribavirin. Among patients with compensated cirrhosis, SVR12 was 93% (40/43) for sofosbuvir/velpatasvir compared to 73% (33/45) for sofosbuvir plus ribavirin. Of the 250 participants who received sofosbuvir/velpatasvir, 43 (16%) had baseline NS5A RASs, of which 88% achieved SVR12 compared to 97% without baseline RASs. Eighty-four percent (21/25) with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of a baseline Y93 substitution, the addition of ribavirin is recommended for patients with cirrhosis.

The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir in genotype 3-infected, noncirrhotic patients who were either treatment-naive or interferon-experienced. Eighty-nine genotype 3 patients received the sofosbuvir/velpatasvir regimen and 97% achieved SVR12 (86/89) (Jacobson, 2017). There were no virologic failures. This confirms the efficacy of sofosbuvir/velpatasvir in genotype 3-infected patients without cirrhosis.

Alternative Regimen

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection. The recommendation is based on ALLY-3, a phase 3 study of the once-daily NS5A inhibitor daclatasvir plus sofosbuvir for 12 weeks among genotype 3-infected, treatment-naive or -experienced (interferon ± ribavirin, sofosbuvir plus ribavirin, or other anti-HCV agents) patients. The study included 101 treatment-naive patients and demonstrated an SVR12 rate of 90%. Among treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12; in treatment-naive patients with compensated cirrhosis (Metavir F4), 58% achieved SVR12 (Nelson, 2015). This suggests that patients with genotype 3 infection and compensated cirrhosis are likely to benefit from an extension of therapy.

Baseline NS5A RASs significantly reduce SVR12 rates with a 12-week course of daclatasvir/sofosbuvir in genotype 3-infected patients. In an analysis of 175 genotype 3-infected patients with nucleotide sequence data from the ALLY-3 trial, the presence of a NS5A Y93H was associated with a reduced SVR12 rate; 54% (7/13) in those with the substitution compared to 92% (149/162) in those without it (Nelson, 2015). Although the small numbers make interpretation difficult, only 7% of participants (13/175) had NS5A Y93H, all of which were subtype 3a. SVR rates were numerically lower among those with both cirrhosis and Y93H. In noncirrhotic patients with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) among noncirrhotics without Y93H. In those with both cirrhosis and Y93H, 25% (1/4) achieved SVR12 compared to 71% (24/34) in those with cirrhosis but without the Y93H substitution (Daklinza PI).

Substitutions A30K, L31F, L31I in the genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daklinza PI). In the ALLY-3 trial, participants with A30K and without cirrhosis achieved 100% SVR12 (9/9); those with compensated cirrhosis had lower SVR12 rates (1/5); (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 patients had compound substitutions with Y93H. Pending further data on optimal therapy, the addition of ribavirin for patients with cirrhosis is recommended in the setting of a baseline Y93 substitution.

ENDURANCE-3 was a randomized (2:1) trial comparing 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg), administered as three 100 mg/40 mg fixed-dose combination pills, to 12 weeks of daclatasvir/sofosbuvir among 348 treatment-naive participants with genotype 3 infection without cirrhosis. In the 115 patients randomized to daclatasvir/sofosbuvir, 97% achieved SVR12, and 20 of 21 participants (95%) with baseline NS5A RAS achieved SVR (Foster, 2017).

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Treatment-Naive Genotype 3 With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 3 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)[c]	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) when Y93H is present	12 weeks	IIa, B
Daily daclatasvir (60 mg)[d] plus sofosbuvir (400 mg) with or without weight-based ribavirin[c]	24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] RAS testing for Y93H is recommended for cirrhotic patients. If present, ribavirin should be included in the regimen or sofosbuvir/velpatasvir/voxilaprevir should be considered.
[d] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Glecaprevir/Pibrentasvir

SURVEYOR-II—a partially randomized, open-label, multicenter, 4-part, phase 2 trial—compared 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg), administered as three 100 mg/40 mg fixed-dose combination pills, to glecaprevir/pibrentasvir plus ribavirin among 48 treatment-naive, genotype 3-infected participants with compensated cirrhosis. All patients treated with 12 weeks of glecaprevir/pibrentasvir, with or without ribavirin, achieved SVR12 (Kwo, 2016b). The presence of baseline NS3 and/or NS5A RASs had no impact on SVR12 rate regardless of inclusion of ribavirin in the treatment regimen; however the analysis was limited because few patients had NS5A RASs. These data indicate that 12 weeks of glecaprevir/pibrentasvir yields high SVR12 rates among treatment-naive, genotype 3-infected patients with compensated cirrhosis.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 3 infection in patients without cirrhosis or with compensated cirrhosis. ASTRAL-3 randomized

552 treatment-naive and -experienced patients (without cirrhosis or with compensated cirrhosis) to 12 weeks of sofosbuvir/velpatasvir or 24 weeks sofosbuvir plus ribavirin (Foster, 2015a). Among those with compensated cirrhosis, the SVR12 was 93% (40/43) in the sofosbuvir/velpatasvir arm compared to 73% (33/45) among those in the sofosbuvir plus ribavirin arm. Of the 250 participants who received sofosbuvir/velpatasvir, 43 (16%) had baseline NS5A RASs, of which 88% achieved SVR12 compared to 97% without baseline substitutions. Eighty-four percent (21/25) of those with Y93H achieved SVR12. Pending further data on optimal therapy in the setting of a baseline Y93 substitution, the addition of ribavirin is recommended for patients with compensated cirrhosis.

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir/velpatasvir among 219 DAA-naive participants with genotype 3 infection and cirrhosis (Jacobson, 2017). The SVR12 rate was 96% in both arms; 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir achieved SVR. Four participants in the sofosbuvir/velpatasvir arm had the Y93H substitution; all achieved SVR12.

Alternative Regimens

Sofosbuvir/Velpatasvir/Voxilaprevir

POLARIS-3 was a randomized, phase 3 trial that compared 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) to 12 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg) among 219 DAA-naive participants with genotype 3 infection and cirrhosis (Jacobson, 2017). Thirty-one percent of participants were interferon treatment experienced. The SVR12 rate was 96% in both arms, 106/110 of patients randomized to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir and 105/109 of those randomized to 12 weeks of sofosbuvir/velpatasvir. There were 2 virologic failures in each arm (2 relapses in the sofosbuvir/velpatasvir/voxilaprevir arm; 1 virologic breakthrough and 1 relapse in the sofosbuvir/velpatasvir arm). Baseline RASs had no effect on treatment response. Among the 6 participants with Y93H in the sofosbuvir/velpatasvir/voxilaprevir arm and 4 in the sofosbuvir/velpatasvir arm, all achieved SVR12. Additionally, no patients receiving sofosbuvir/velpatasvir/voxilaprevir with virologic failure developed RASs. Although an 8-week regimen was studied in POLARIS-3, a 12-week regimen of sofosbuvir/velpatasvir/voxilaprevir was approved by the FDA for the indication of retreatment of DAA-experienced patients and could be considered as an alternative regimen for patients with cirrhosis and Y93H.

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks was approved by the FDA for treatment of genotype 3 infection. The recommendation is based on ALLY-3, a phase 3 study of daclatasvir/sofosbuvir for 12 weeks among genotype 3-infected, treatment-naive or -experienced (interferon ± ribavirin, sofosbuvir plus ribavirin, or other anti-HCV agents) patients. The study included 101 treatment-naive patients and demonstrated an SVR12 rate of 90%. In treatment-naive patients without cirrhosis (Metavir F0-F3), 97% achieved SVR12, compared to 58% SVR12 in treatment-naive patients with cirrhosis (Metavir F4) (Nelson, 2015).

The results of the ALLY-3 study suggest that patients with genotype 3 infection and cirrhosis are likely to benefit from an extension of therapy. This has been confirmed in cohort studies, including the European compassionate-use program, which reported SVR12 rates of 70% vs 86% when daclatasvir/sofosbuvir was used for 12 weeks and 24 weeks in genotype 3-infected patients with cirrhosis, respectively. The role of ribavirin could not be clarified as only 4 patients received daclatasvir/sofosbuvir plus ribavirin for 12 weeks, all of which achieved SVR12. SVR12 was comparable between the 24-week arms irrespective of the addition of ribavirin (85.9% [116/135] without ribavirin; 81.3% [39/48] with ribavirin). SVR12 rates were also higher in those with compensated Child-Pugh A cirrhosis (85% to 90%) compared to 70.6% in Child-Pugh B/C. Again, the addition of ribavirin did not increase SVR12 rates in the 24-week treatment arms (Hézode, 2017). Seventy-three percent of patients were treatment-experienced, however earlier data suggested that SVR12 rates were higher in treatment-naive patients (91% to 100%) compared to treatment-experienced (81% to 82%). SVR12 rates were similar in patients who received ribavirin (88%, 29/33) and those who did not (86%, 42/49) (Hézode, 2017).

Baseline NS5A RASs significantly reduce SVR12 rates with a 12-week course of daclatasvir/sofosbuvir in genotype 3-infected patients. In an analysis of 175 genotype 3-infected patients with nucleotide sequence data from the ALLY-3 trial, the presence of a NS5A Y93H was associated with a reduced SVR12 rate; 54% (7/13) in those with the substitution compared to 92% in those without it (149/162). Although the small numbers make interpretation difficult, only 7% of participants (13/175) had NS5A Y93H, all of which were subtype 3a. SVR rates were numerically lower among those with both cirrhosis and Y93H. In noncirrhotic patients with Y93H, 67% (6/9) achieved SVR12 compared to 98% (125/128) among noncirrhotics without Y93H. In those with both cirrhosis and Y93H, 25% (1/4) achieved SVR12 compared to 71% (24/34) in those with cirrhosis but without the Y93H substitution (Daklinza PI, 2016).

Substitutions A30K, L31F, L31I in the genotype 3a replicon are associated with reduced daclatasvir susceptibility (Daklinza PI, 2016). In the ALLY-3 trial, participants with A30K and without cirrhosis achieved 100% SVR12 (9/9); those with cirrhosis had lower SVR12 rates (1/5) (Nelson, 2015). The impact of this single substitution is difficult to discern as 2/5 patients had compound substitutions with Y93H. Pending further data on optimal therapy, the addition of ribavirin for patients with cirrhosis is recommended in the setting of a baseline Y93 substitution.

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Treatment-Naive Genotype 4

The following pages include guidance for management of treatment-naive patients with genotype 4 infection.

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Treatment-Naive Genotype 4 Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: Treatment-Naive Genotype 4 Patients Without Cirrhosis		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin	12 weeks	I, A
[a] This is a 3-tablet coformulation. Please refer to the prescribing information.		

Recommended Regimens

Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in part 4 of the phase 2 SURVEYOR-2 study (100% SVR12 in 34 patients with genotype 4, 5, or 6) (Kwo, 2017b), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills (Asselah, 2016). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week versus 12-week course of glecaprevir/pibrentasvir for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis (Hassanein, 2016). In the intention-to-treat analysis, 43/46 with genotype 4, 2/2 with genotype 5, and 9/10 with genotype 6 achieved SVR 12; there were no known virologic failures.

EXPEDITION-1 investigated use of glecaprevir/pibrentasvir in treatment-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 99% (145/146) achieved SVR12, including 16/16 (100%) with genotype 4, 2/2 (100%) with genotype 5, and 7/7 (100%) with genotype 6 (Forns, 2017). Based on these studies, glecaprevir/pibrentasvir was approved for treatment of genotype 4-infected, DAA-naive, noncirrhotic patients for a duration of 8 weeks.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 4 infection in patients with or without cirrhosis. ASTRAL-1 included 64 genotype 4-infected, treatment-naive patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) (Feld, 2015).

The POLARIS-2 phase 3 study randomized DAA-naive patients to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) versus 12 weeks of sofosbuvir/velpatasvir. Of 57 patients with genotype 4 in the sofosbuvir/velpatasvir arm, 98% achieved SVR and 1 patient experienced relapse (Jacobson, 2017).

Elbasvir/Grazoprevir

A phase 2/3 trial evaluated 66 treatment-naive, genotype 4 patients treated with daily elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks. Ten patients had weight-based ribavirin added to the regimen and 56 did not. Six participants (9.1%) were cirrhotic and 28 (42.4%) had HIV/HCV coinfection. Overall, 97% (64/66) achieved SVR12. There was 1 treatment failure and 1 patient was lost to follow-up. The impact of ribavirin could not be assessed, however the addition of ribavirin numerically increased the SVR12 rate in treatment-experienced participants. Baseline RASs and genotype subtype did not appear to impact SVR12 rates (Asselah, 2015).

Ledipasvir/Sofosbuvir

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) in 21 genotype 4-infected patients, of whom 60% were treatment naive and 43% had advanced fibrosis (Metavir stage F3 or F4) (Kohli, 2015). One patient took the first dose and then withdrew consent. The 20 patients who completed treatment all achieved SVR12; thus, the SVR12 rate was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Abergel and colleagues reported data from an open-label, single-arm study including 22 genotype 4-infected, treatment-naive patients (1 with cirrhosis) with an SVR12 rate of 95% (21/22) (Abergel, 2016). These pilot studies support the use of ledipasvir/sofosbuvir in patients with genotype 4 infection.

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

PEARL-I was a randomized, open-label, phase 2b study that included a cohort of 86 treatment-naive patients with genotype 4 infection without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg), with or without weight-based ribavirin. SVR12 rates were 100% (42/42) in the ribavirin arm and 90.9% (40/44) in the group not receiving ribavirin. Adverse effects were generally mild, with headache, asthenia, fatigue, and nausea most commonly reported. There were no discontinuations owing to adverse events (Hézode, 2015).

The AGATE-I trial randomized 120 treatment-naive and -experienced patients with genotype 4 infection and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a). Similarly, the AGATE-II trial offered 100 treatment-naive and -experienced (interferon-based regimens) noncirrhotic patients with genotype 4 infection paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. These data support the use of a 12-week course of paritaprevir/ritonavir/ombitasvir plus ribavirin in treatment-experienced genotype 4 patients (Esmat, 2015).

Last update: September 21, 2017

Treatment-Naive Genotype 4 With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: Treatment-Naive Genotype 4 Patients With Compensated Cirrhosis[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) and weight-based ribavirin[c]	12 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Please see statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Recommended Regimens

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 4 infection in patients with or without cirrhosis. ASTRAL-1 included 64 genotype 4-infected, treatment-naive patients without cirrhosis or with compensated cirrhosis, all of whom achieved SVR12 (100%) (Feld, 2015).

The POLARIS-2 phase 3 study randomized DAA-naive patients (19% with compensated cirrhosis, overall) to 8 weeks of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) or 12 weeks of sofosbuvir/velpatasvir. Of 57 patients with genotype 4 in the sofosbuvir/velpatasvir arm, 98% achieved SVR and 1 patient experienced relapse (Jacobson, 2017).

Glecaprevir/Pibrentasvir

EXPEDITION-1 was a multicenter, open-label, single-arm, phase 3 trial that enrolled 146 treatment-naive or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Patients received the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks. Across all genotypes, 145/146 (99%) achieved SVR12 (Forns, 2017). EXPEDITION-1 included 16 treatment-naive and -experienced genotype 4-infected participants with compensated cirrhosis. All 16 patients achieved SVR12. Baseline NS5A RASs were detected by next-generation sequencing (using a 15% detection cutoff) in 40% of 133 tested

participants. Baseline NS5A RASs had no effect on SVR rates among treatment-naive and -experienced participants with genotype 4. Based on this study, a 12-week course of glecaprevir/pibrentasvir is recommended for genotype 4-infected, *treatment-naive patients with compensated cirrhosis.*

Elbasvir/Grazoprevir

A phase 2/3 trial evaluated 66 treatment-naive, genotype 4 patients treated with daily elbasvir (50 mg)/grazoprevir (100 mg) for 12 weeks. Ten patients had weight-based ribavirin added to the regimen and 56 did not. Six participants (9.1%) were cirrhotic and 28 (42.4%) had HIV/HCV coinfection. Overall, 97% (64/66) achieved SVR12. There was 1 treatment failure and 1 patient was lost to follow-up. The impact of ribavirin could not be assessed, however the addition of ribavirin numerically increased the SVR12 rate in treatment-experienced participants. Baseline RASs and subtype did not appear to impact SVR12 rates (Asselah, 2015).

Ledipasvir/Sofosbuvir

The SYNERGY trial was an open-label study evaluating 12 weeks of ledipasvir (90 mg)/sofosbuvir (400 mg) in 21 genotype 4-infected patients, of whom 60% were treatment naive and 43% had advanced fibrosis (Metavir stage F3 or F4) (Kohli, 2015). One patient took the first dose and then withdrew consent. The 20 patients who completed treatment all achieved SVR12; thus, the SVR12 rate was 95% in the intention-to-treat analysis and 100% in the per-protocol analysis. Abergel and colleagues reported data from an open-label, single-arm study including 22 genotype 4-infected, treatment-naive patients (1 with cirrhosis) with an SVR12 rate of 95% (21/22) (Abergel, 2016). These pilot studies support the use of ledipasvir/sofosbuvir in patients with genotype 4 infection.

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

PEARL-I was a randomized, open-label phase 2b study that included a cohort of 86 treatment-naive patients with genotype 4 infection without cirrhosis who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg), with or without weight-based ribavirin. SVR12 rates were 100% (42/42) in the ribavirin arm and 90.9% (40/44) in the group not receiving ribavirin. Adverse effects were generally mild, with headache, asthenia, fatigue, and nausea most commonly reported. There were no discontinuations owing to adverse events (Hézode, 2015).

The AGATE-I trial randomized 120 treatment-naive and -experienced patients with genotype 4 infection and compensated cirrhosis to receive 12 weeks or 16 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 rates in the 12-week and 16-week arms were 96% and 100%, respectively. The regimens were well tolerated (Asselah, 2015a). Similarly, the AGATE-II trial offered 100 treatment-naive and -experienced (interferon-based regimens) noncirrhotic patients with genotype 4 infection paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin for 12 weeks. The SVR12 was 94%. Additionally, AGATE-II randomized 60 treatment-naive and -experienced genotype 4-infected patients with compensated cirrhosis to receive either 12 or 24 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR rate from the 12-week arm was 97%. These data support the use of a 12-week course of paritaprevir/ritonavir/ombitasvir plus ribavirin in treatment-experienced genotype 4 patients, including those with cirrhosis (Esmat, 2015).

Last update: September 21, 2017

Treatment-Naive Genotype 5 or 6

Recommended regimens listed by evidence level and alphabetically for:

Treatment-Naive Genotype 5 or 6 Patients With and Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)[b]	8 weeks (no cirrhosis)	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/ pibrentasvir (120 mg)[b]	12 weeks (cirrhosis)	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Glecaprevir/Pibrentasvir

Based on favorable data for 12 weeks of treatment for noncirrhotic patients in the phase 2 SURVEYOR-2 study (100% SVR12 in 34 patients with genotype 4, 5, or 6) (Kwo, 2017b), ENDURANCE-4 enrolled 121 DAA-naive or -experienced (sofosbuvir plus ribavirin ± peginterferon) genotype 4, 5, or 6 patients without cirrhosis to receive 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg pills (Asselah, 2016). Of those enrolled, 86% had fibrosis stage F0 to F1 and 68% were treatment naive. The genotype distribution was 63% genotype 4, 21% genotype 5, and 16% genotype 6. The overall SVR12 rate for the intention-to-treat population was 99% (120/121), including 99% (75/76) for genotype 4, 100% for genotype 5 (26/26), and 100% (19/19) for genotype 6.

Genotype 4, 5, and 6 patients were not included in the randomized study to compare an 8-week vs 12-week course for DAA-naive, noncirrhotic patients. However, part 4 of the SURVEYOR-2 study investigated an 8-week course of glecaprevir/pibrentasvir in DAA-naive patients without cirrhosis (Hassanein, 2016). In the intention-to-treat analysis, 2/2 with genotype 5 and 9/10 with genotype 6 achieved SVR 12; there were no known virologic failures.

In addition, EXPEDITION-1 investigated the use of glecaprevir/pibrentasvir in DAA-naive (75%) or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) patients with compensated cirrhosis. Of 146 patients with genotype 1, 2, 4, 5, or 6 given 12 weeks of glecaprevir/pibrentasvir, 99% (145/146) achieved SVR12, including 2/2 with genotype 5 and 7/7 with genotype 6 (Forns, 2017). Based on these studies, glecaprevir/pibrentasvir was approved for an 8-week course (noncirrhotic) and 12-week course (cirrhotic) of treatment for people with genotype 5 or genotype 6 infection.

Sofosbuvir/Velpatasvir

The daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks was approved by the FDA for the treatment of genotype 5 and 6 infection in patients with and without cirrhosis (Feld, 2015). ASTRAL-1 included 24 genotype 5 treatment-naive participants with and without cirrhosis, 23 (96%) of whom achieved SVR12. The study also included 38 genotype 6 treatment-naive participants with and without cirrhosis, all of whom achieved SVR12 (100%). An additional 9 genotype 6 patients received sofosbuvir/velpatasvir in the POLARIS-2 phase 3 study, all of whom achieved SVR (Jacobson, 2017).

Ledipasvir/Sofosbuvir

Although there are limited data on patients with genotype 5 infection, the in vitro activity of sofosbuvir and ledipasvir are quite good with EC_{50} of 15 nM and 0.081 nM, respectively. Abergel and colleagues reported data from an open-label, single-arm study that included 41 genotype 5-infected patients with an overall SVR12 rate of 95% (39/41) (Abergel, 2016). The SVR12 rate was also 95% specifically in treatment-naive patients (20/21), of whom only 3 had cirrhosis but all achieved SVR12.

Ledipasvir has in vitro activity against most genotype 6 subtypes, except for 6e (Wong, 2013); (Kohler, 2014). A small, 2-center, open-label study (NCT01826981) investigated the safety and in vivo efficacy of ledipasvir/sofosbuvir for 12 weeks in treatment-naive and -experienced patients with genotype 6 infection. Twenty-five patients (92% were treatment-naive) who were primarily Asian (88%) had infection from 7 different subtypes (32% 6a; 24% 6e; 12% 6l; 8% 6m; 12% 6p; 8% 6q; 4% 6r). Two patients (8%) had cirrhosis. The SVR12 rate was 96% (24/25), and the single patient who experienced relapse had discontinued therapy at week 8 because of drug use. No patient discontinued treatment owing to adverse events (Gane, 2015).

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Retreatment of Persons in Whom Prior Therapy Failed

This section provides guidance on the retreatment of persons with chronic HCV infection in whom prior therapy failed. The level of the evidence available to inform the best regimen for each patient and the strength of the recommendation vary, and are rated accordingly (see Methods Table 2). In addition, specific recommendations are given when treatment differs for a particular group (eg, those infected with different viral genotypes). Recommended regimens are those that are favored for most patients in that group, based on optimal efficacy, favorable tolerability and toxicity profiles, complexity, and duration.

Alternative regimens are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data. In certain situations, an alternative regimen may be optimal for a specific patient.

Not recommended regimens are clearly inferior compared to recommended and alternative regimens due to factors such as lower efficacy, unfavorable tolerability and toxicity, longer treatment duration, and/or higher pill burden. Unless otherwise indicated, such regimens should not be administered to patients with HCV infection.

Specific considerations for pediatric patients and persons with HIV/HCV coinfection, decompensated cirrhosis (moderate or severe hepatic impairment; Child-Turcotte-Pugh [CTP] class B or C), HCV infection post liver transplantation, and severe renal impairment, end-stage renal disease (ESRD), or HCV infection post kidney transplantation are addressed in other sections of the guidance.

Recommended and alternative regimens are listed in order of level of evidence. When several regimens are at the same recommendation level, they are listed in alphabetical order. Regimen choice should be determined based on patient-specific data, including drug interactions. Patients receiving antiviral therapy require careful pretreatment assessment for comorbidities that may influence treatment response. All patients require careful monitoring during treatment, particularly for anemia if ribavirin is included in the regimen (See Monitoring section).

Mixed Genotypes

Rarely, genotyping assays may indicate the presence of a mixed infection (eg, genotypes 1a and 2). Treatment data for mixed genotypes with direct-acting antivirals (DAAs) are sparse but utilization of a pangenotypic regimen should be considered. When the correct combination or duration of treatment is unclear, expert consultation should be sought.

The following pages include guidance for management of treatment-experienced patients.

- Genotype 1
- Genotype 2
- Genotype 3
- Genotype 4
- Genotype 5 or 6

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Treatment-Experienced Genotype 1

Multiple highly potent, DAA combination regimens are recommended for patients with genotype 1 infection. There are differences in the recommended regimens based on viral subtype, the presence or absence of baseline NS5A resistance-associated substitutions (RASs), the presence or absence of compensated cirrhosis, and the type of prior failed regimen(s). Genotype 1 infection that cannot be subtyped should be treated as genotype 1a infection.

Approximately 10% to 15% of genotype 1-infected patients without prior exposure to NS5A inhibitors have detectable NS5A RASs prior to treatment. The clinical impact of NS5A RASs varies across regimens and baseline patient characteristics. In patients with genotype 1a infection, the presence of baseline NS5A RASs that cause a large reduction in the activity of NS5A inhibitors (>5 fold) adversely impacts response to some NS5A inhibitor-containing regimens (Zeuzem, 2017); (Jacobson, 2015b). These RASs are found by population sequencing in roughly 5% to 10% of patients; relevant RASs vary by DAA regimen. Given that baseline NS5A RASs are one of the strongest pretreatment predictors of therapeutic outcome with certain regimens in genotype 1a-infected patients, testing for these RASs prior to deciding on a therapeutic course is recommended in selected situations (Zeuzem, 2015c). For further guidance please see the Resistance Primer section.

Compared to interferon-based therapy, DAAs are associated with an increased risk of drug interactions with concomitant medications. With combinations of DAAs in the various treatment regimens, attention to drug-drug interactions is that much more important (see Drug Interactions table). The product prescribing information and other resources (eg, http://www.hep-druginteractions.org) should be consulted regularly to ensure safety when prescribing DAA regimens. Important interactions with commonly used medications (eg, antacids, lipid-lowering drugs, anti-epileptics, antiretrovirals, etc) exist for all regimens discussed.

The following pages include guidance for management of treatment-experienced patients with genotype 1 infection.

- Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis
- Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis
- Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis
- Peginterferon/Ribavirin-Experienced, Genotype 1b Patients With Compensated Cirrhosis
- NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis
- NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients With Compensated Cirrhosis
- Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients Without Cirrhosis
- Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients With Compensated Cirrhosis
- NS5A Inhibitor DAA-Experienced Genotype 1 Patients

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 1a Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[a] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg), and weight-based ribavirin	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with baseline NS5A RASs[a] for elbasvir	16 weeks	IIa, B

[a] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Elbasvir/Grazoprevir

The phase 3 C-EDGE TE trial evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) in patients with a prior peginterferon/ribavirin treatment failure. Patients were randomized to elbasvir/grazoprevir for 12 weeks or 16 weeks, with or without ribavirin. Genotype 1-infected patients treated for 12 weeks without ribavirin had an overall SVR12 rate of 93.8% (90/96), which was nearly identical to the rate seen in those treated for 12 weeks with ribavirin (94.4%, 84/89) (Kwo, 2017). SVR rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a-infected patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-infected patients with baseline NS5A RASs (>5 fold), only 52% (11/21) achieved SVR due to a higher relapse rate (Kwo, 2015).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) (Zeuzem, 2017). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR, compared to 96% (52/54) among those without these baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen (Jacobson, 2015b).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended for genotype 1a-infected patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Glecaprevir/Pibrentasvir

The phase 3 ENDURANCE-1 trial enrolled 703 treatment-naive or -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 1 infection without cirrhosis. Participants were randomized to 8 weeks or 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills (Zeuzem, 2016). Of those enrolled, 43% had genotype 1a infection, 85% had fibrosis stage F0 or F1, and 38% were treatment experienced. Ninety-nine percent of the treatment-experienced patients had previously received interferon-based therapy and 1% had received sofosbuvir-based treatment. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority. A single patient experienced on-treatment virologic failure (genotype 1a, day 29). There were no documented relapses in either study arm. This regimen was well tolerated with rare adverse events leading to discontinuation (0.1%); no significant laboratory abnormalities were noted.

Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) has been evaluated in patients without cirrhosis and a history of treatment failure with peginterferon/ribavirin, with or without HCV protease inhibitors (telaprevir or boceprevir). In the ION-2 study, patients who had not responded to prior peginterferon/ribavirin therapy were treated with ledipasvir/sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In the population without cirrhosis, the overall SVR rate was 98%. Specifically, in patients without cirrhosis and a history of peginterferon/ribavirin failure, 94% (33/35) achieved SVR after 12 weeks of ledipasvir/sofosbuvir treatment, and 100% (38/38) achieved SVR in the ledipasvir/sofosbuvir plus ribavirin study arm (Afdhal, 2014b). This regimen was well tolerated in all groups with no serious adverse events reported for the 12-week regimen, with or without ribavirin.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection who were treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b-infected, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. The regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) vs the placebo group (77%).

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

In the SAPPHIRE-2 study, the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin was investigated for the treatment of patients with genotype 1 infection in whom previous peginterferon/ribavirin therapy failed (Zeuzem, 2014). In this phase 3 trial, patients without cirrhosis who were treated for 12 weeks had an overall SVR rate of 96% (286/297). Response rates did not differ substantially when stratified by subtype (genotype 1a, 96% [166/173]; genotype 1b, 97% [119/123]) or kinetics of prior response to peginterferon/ribavirin (relapse, 95% [82/86]; partial response, 100% [65/65]; null response, 95% [139/146]).

In the PEARL-II study, 179 genotype 1b-infected patients without cirrhosis in whom previous peginterferon/ribavirin therapy failed were treated for 12 weeks with paritaprevir/ritonavir/ombitasvir plus dasabuvir, with or without weight-based ribavirin (Andreone, 2014). The SVR rates were 100% (91/91) in the ribavirin-free arm and 97% (85/88) in the ribavirin-containing arm, supporting the recommendation that this regimen may be used without ribavirin for patients with genotype 1b infection. Due to the complexity of this regimen—which is primarily driven by the need to include weight-based ribavirin for some patients and the drug interaction profile—it is categorized as an alternative regimen, suggesting it remains highly effective but with limitations.

Simeprevir + Sofosbuvir

The phase 3 OPTIMIST-1 study evaluated a 12-week course of daily simeprevir (150 mg) plus sofosbuvir (400 mg) in genotype 1-infected patients who were treatment-naive or -experienced without cirrhosis (Kwo, 2016). Patients were randomized to 8 weeks or 12 weeks of treatment. Superiority in SVR12 was assessed for 12 weeks of simeprevir plus sofosbuvir versus a composite historical control SVR rate. SVR12 in the 12-week arm was 97%, meeting superiority versus the historical control (87%). However, the 8-week arm only achieved an SVR12 rate of 83%, which did not meet superiority versus the historical control. Among those treated for 12 weeks, the SVR rate in peginterferon/ribavirin-experienced patients was 95% (38/40). The SVR rate in patients with genotype 1a infection with a baseline Q80K substitution (96%; 44/46) was similar to that observed in patients without the substitution (97%; 68/70). Although simeprevir plus sofosbuvir is a highly effective regimen, the drug interaction profile with simeprevir and the complexity of accessing this regimen (a combination of 2 different manufacturer's products) makes it an alternative regimen.

Daclatasvir + Sofosbuvir

Two observational, early access programs in the United Kingdom and France have studied the daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) in genotype 1-infected, treatment-experienced patients with a history of peginterferon/ribavirin treatment failure (Foster, 2015); (Pol, 2017); (Foster, 2016). In the French cohort, patients were treated with daclatasvir plus sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In patients treated with daclatasvir plus sofosbuvir alone, a numerically higher rate of sustained virologic response at 4 weeks (SVR4) was seen in those treated for 24 weeks (12 weeks, 82.6% [15/18] vs 24 weeks, 96.1% [75/78]). Patients treated with daclatasvir and

sofosbuvir plus ribavirin had high response rates in the 12-week and 24-week treatment groups (100% and 97.1%, respectively)—but only 4 patients were treated for 12 weeks. The selection of daclatasvir or ledipasvir and the use of ribavirin were at the discretion of the treating physician; most patients (94.4%) had ribavirin in their regimen. Among patients treated with sofosbuvir plus ribavirin for 12 weeks, the SVR rates were 86% for those who received ledipasvir (n=164) and 82% for those who received daclatasvir (n=82).

Based on these limited data, consideration should be given to the addition of ribavirin when working with more difficult-to-treat patients, such as those with compensated cirrhosis. Due to the complexity of accessing this regimen (a combination of 2 different manufacturer's products), this is recommended as an alternative regimen.

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Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 1a Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients without baseline NS5A RASs[b] for elbasvir	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	12 weeks	I, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with baseline NS5A RASs[b] for elbasvir	16 weeks	I, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Elbasvir/Grazoprevir

The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) was evaluated in patients with a history of failed peginterferon/ribavirin therapy in the C-EDGE TE study. In this phase 3 trial, patients were randomized to 12 weeks or 16 weeks of elbasvir/grazoprevir, with or without ribavirin. Genotype 1-infected patients treated for 12 weeks without ribavirin had an overall SVR rate of 93.8% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4%, 84/89) (Kwo, 2017). Response rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96). A subset analysis of patients with compensated cirrhosis revealed similar response rates to the population without cirrhosis when treated with elbasvir/grazoprevir without ribavirin for 12 weeks (SVR with cirrhosis 95% [19/20]; SVR without cirrhosis 94.9% [37/39]).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week

elbasvir/grazoprevir regimen. In genotype 1a-infected patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-infected patients with baseline NS5A RASs (>5 fold), only 52.4% (11/21) achieved SVR due to a higher relapse rate (Kwo, 2015).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) (Zeuzem, 2017). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR compared to 96% (52/54) among those without baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen (Jacobson, 2015b).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended in genotype 1a-infected patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive and -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b-infected, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. This regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) versus the placebo group (77%).

Glecaprevir/Pibrentasvir

The EXPEDITION-1 trial investigated use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks in 146 patients with compensated cirrhosis infected with genotype 1, 2, 4, 5, or 6. Twenty-five percent (36/146) of enrolled patients were non-DAA treatment experienced. SVR12 was 98.9% (89/90) among genotype1-infected patients. The single treatment failure occurred in a patient with genotype 1a infection who relapsed at post-treatment week 8 (Forns, 2017). Ninety-one percent of patients (133/146) had a Child-Pugh score of 5 and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count <100 x 10^9/L and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. Glecaprevir/pibrentasvir is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

Alternative Regimens

Ledipasvir/Sofosbuvir + Ribavirin

The double-blind, placebo-controlled, phase 2 SIRIUS trial enrolled genotype 1-infected patients with compensated cirrhosis who did not achieve SVR with peginterferon/ribavirin plus telaprevir or boceprevir. Participants were randomized

to either 12 weeks of placebo followed by 12 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin, or ledipasvir/sofosbuvir plus placebo for 24 weeks. The SVR rates were similar in the study arms: 96% (74/77) in the group that received ledipasvir/sofosbuvir plus ribavirin for 12 weeks (3 relapses), and 97% (75/77) in the group that received ledipasvir/sofosbuvir for 24 weeks (2 relapses) (Bourliere, 2015).

These findings are further supported by a post hoc analysis of treatment-naive or -experienced, genotype 1-infected patients with compensated cirrhosis who were treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies (including the SIRIUS trial). In this analysis, ledipasvir/sofosbuvir for 12 weeks was inferior to ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Safety and tolerability were similar in the groups and, apart from anemia, reported adverse events did not differ substantially between patients treated with or without ribavirin (Reddy, 2015). Due to the need for ribavirin, this regimen is recommended as an alternative for genotype 1-infected patients with a history of peginterferon/ribavirin failure who have compensated cirrhosis.

Baseline NS5A RASs adversely impact response to ledipasvir/sofosbuvir therapy. The magnitude of impact varies based on several factors, including virus (genotype subtype, specific RAS); regimen (companion drugs, use of ribavirin); and patient factors (treatment experience, presence of cirrhosis). In an analysis of more than 350 genotype 1-infected, treatment-experienced patients with cirrhosis, the presence of baseline ledipasvir RASs (defined as RASs resulting in a >2.5-fold shift in ledipasvir EC_{50}) detected at a 1% level resulted in a lower SVR12 rate compared to those without baseline RASs (Zeuzem, 2017). The SVR12 rates were 89% with RASs versus 96% in the absence of RASs with a 12-week course of ledipasvir/sofosbuvir plus ribavirin, and 87% versus 100%, respectively, with a 24-week course of ledipasvir/sofosbuvir without ribavirin. The impact of baseline RASs is likely greater in a genotype 1a only population.

Given the vulnerable nature of this population, baseline NS5A resistance testing should be considered for genotype 1a-infected, treatment-experienced patients with compensated cirrhosis prior to use of ledipasvir/sofosbuvir. If ledipasvir-associated RASs are detected, a different regimen should be used to optimize treatment response.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The TURQUOISE-III study evaluated the safety and efficacy of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) without ribavirin for 12 weeks in patients with genotype 1b infection and compensated cirrhosis. Sixty patients were enrolled (62% men; 55% treatment experienced; 83% with the IL28B non-CC genotype; 22% with a platelet count <90 x 10^9/L; and 17% with an albumin level <3.5 g/dL). All patients completed treatment and achieved SVR12 (Feld, 2016). Based on this study, treating patients with genotype 1b infection with paritaprevir/ritonavir/ombitasvir plus dasabuvir without ribavirin is ranked as an alternative regimen (primarily because of drug interactions), regardless of prior treatment experience or the presence of compensated cirrhosis.

The US Food and Drug Administration (FDA) released a warning in October 2015 regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.)
Paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with Child-Turcotte-Pugh (CTP) class B or class C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported the rapid onset of liver injury and, in some cases, hepatic decompensation in patients with cirrhosis—including CTP class A compensated cirrhosis and decompensated cirrhosis—who were receiving paritaprevir/ritonavir/ombitasvir ± dasabuvir. The liver injury and decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir resulted in resolution of the hepatic injury. However, some patients (including at least 2 persons with CTP class A compensated cirrhosis) died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and, in many cases, its resolution with discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir suggest drug-induced liver injury. Although paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with CTP class B or class C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.

For patients with CTP class A cirrhosis, the unlikely but real possibility of drug-induced liver injury should be discussed with the patient. If the decision is made to initiate treatment with paritaprevir/ritonavir/ombitasvir ± dasabuvir, close monitoring of total and direct bilirubin and transaminase levels every 1 to 2 weeks for the first 4 weeks of therapy is recommended to ensure early detection of drug-induced liver injury. Educating patients about the importance of reporting systemic symptoms, such as jaundice, weakness, and fatigue, is also strongly recommended. The regimen should be discontinued immediately if drug-induced liver injury is suspected. If a patient is already taking paritaprevir/ritonavir/ombitasvir ± dasabuvir and tolerating the regimen, laboratory monitoring as noted without discontinuation of treatment is recommended unless there are signs or symptoms of liver injury. If heightened monitoring cannot be provided during the first 4 weeks of therapy with paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with compensated cirrhosis, use of these regimens is not recommended.

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 1b Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)	12 weeks	I, A
Daily simeprevir (150 mg) plus sofosbuvir (400 mg)	12 weeks	I, A
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	12 weeks	I, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Elbasvir/Grazoprevir

The phase 3 C-EDGE TE trial evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) in patients with a prior peginterferon/ribavirin treatment failure. Patients were randomized to elbasvir/grazoprevir for 12 weeks or 16 weeks, with or without ribavirin. Genotype 1-infected patients treated for 12 weeks without ribavirin had an overall SVR12 rate of 93.8% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4%, 84/89) (Kwo, 2017). SVR rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week elbasvir/grazoprevir regimen. In genotype 1a-infected patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-infected patients with baseline NS5A RASs (>5 fold), only 52% (11/21) achieved SVR due to a higher relapse rate (Kwo, 2015).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) (Zeuzem, 2017). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR, compared to 96% (52/54) among those without these baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen (Jacobson, 2015b).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended for genotype 1a-infected patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Glecaprevir/Pibrentasvir

The phase 3 ENDURANCE-1 trial enrolled 703 treatment-naive or -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) with genotype 1 infection without cirrhosis. Participants were randomized to 8 weeks or 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills (Zeuzem, 2016). Of those enrolled, 43% had genotype 1a infection, 85% had fibrosis stage F0 or F1, and 38% were treatment experienced. Ninety-nine percent of the treatment-experienced patients had previously received interferon-based therapy and 1% had received sofosbuvir-based treatment. Overall SVR12 rates for the intention-to-treat population were 99% (348/351) in the 8-week arm and 99.7% (351/352) in the 12-week arm. The 8-week arm met the predefined study criteria for noninferiority. A single patient experienced on-treatment virologic failure (genotype 1a, day 29). There were no documented relapses in either study arm. This regimen was well tolerated with rare adverse events leading to discontinuation (0.1%); no significant laboratory abnormalities were noted.

Ledipasvir/Sofosbuvir

The daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) has been evaluated in patients without cirrhosis and a history of treatment failure with peginterferon/ribavirin, with or without HCV protease inhibitors (telaprevir or boceprevir). In the ION-2 study, patients who had not responded to prior peginterferon/ribavirin therapy were treated with ledipasvir/sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In the population without cirrhosis, the overall SVR rate was 98%. Specifically, in patients without cirrhosis and a history of peginterferon/ribavirin failure, 94% (33/35) achieved SVR after 12 weeks of ledipasvir/sofosbuvir treatment, and 100% (38/38) achieved SVR in the ledipasvir/sofosbuvir plus ribavirin study arm (Afdhal, 2014b). This regimen was well tolerated in all groups with no serious adverse events reported for the 12-week regimen, with or without ribavirin.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection who were treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. Among

patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b-infected, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. The regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) vs the placebo group (77%).

Alternative Regimens

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

In the SAPPHIRE-2 study, the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) with weight-based ribavirin was investigated for the treatment of patients with genotype 1 infection in whom previous peginterferon/ribavirin therapy failed (Zeuzem, 2014). In this phase 3 trial, patients without cirrhosis who were treated for 12 weeks had an overall SVR rate of 96% (286/297). Response rates did not differ substantially when stratified by subtype (genotype 1a, 96% [166/173]; genotype 1b, 97% [119/123]) or kinetics of prior response to peginterferon/ribavirin (relapse, 95% [82/86]; partial response, 100% [65/65]; null response, 95% [139/146]).

In the PEARL-II study, 179 genotype 1b-infected patients without cirrhosis in whom previous peginterferon/ribavirin therapy failed were treated for 12 weeks with paritaprevir/ritonavir/ombitasvir plus dasabuvir, with or without weight-based ribavirin (Andreone, 2014). The SVR rates were 100% (91/91) in the ribavirin-free arm and 97% (85/88) in the ribavirin-containing arm, supporting the recommendation that this regimen may be used without ribavirin for patients with genotype 1b infection. Due to the complexity of this regimen—which is primarily driven by the need to include weight-based ribavirin for some patients and the drug interaction profile—it is categorized as an alternative regimen, suggesting it remains highly effective but with limitations.

Simeprevir + Sofosbuvir

The phase 3 OPTIMIST-1 study evaluated a 12-week course of daily simeprevir (150 mg) plus sofosbuvir (400 mg) in genotype 1-infected patients who were treatment-naive or -experienced without cirrhosis (Kwo, 2016). Patients were randomized to 8 weeks or 12 weeks of treatment. Superiority in SVR12 was assessed for 12 weeks of simeprevir plus sofosbuvir versus a composite historical control SVR rate. SVR12 in the 12-week arm was 97%, meeting superiority versus the historical control (87%). However, the 8-week arm only achieved an SVR12 rate of 83%, which did not meet superiority versus the historical control. Among those treated for 12 weeks, the SVR rate in peginterferon/ribavirin-experienced patients was 95% (38/40). The SVR rate in patients with genotype 1a infection with a baseline Q80K substitution (96%; 44/46) was similar to that observed in patients without the substitution (97%; 68/70). Although simeprevir plus sofosbuvir is a highly effective regimen, the drug interaction profile with simeprevir and the complexity of accessing this regimen (a combination of 2 different manufacturer's products) makes it an alternative regimen.

Daclatasvir + Sofosbuvir

Two observational, early access programs in the United Kingdom and France have studied the daily combination of daclatasvir (60 mg) plus sofosbuvir (400 mg) in genotype 1-infected, treatment-experienced patients with a history of peginterferon/ribavirin treatment failure (Foster, 2015); (Pol, 2017); (Foster, 2016). In the French cohort, patients were treated with daclatasvir plus sofosbuvir, with or without ribavirin, for 12 weeks or 24 weeks. In patients treated with daclatasvir plus sofosbuvir alone, a numerically higher rate of sustained virologic response at 4 weeks (SVR4) was seen in those treated for 24 weeks (12 weeks, 82.6% [15/18] vs 24 weeks, 96.1% [75/78]). Patients treated with daclatasvir and sofosbuvir plus ribavirin had high response rates in the 12-week and 24-week treatment groups (100% and 97.1%, respectively)—but only 4 patients were treated for 12 weeks. The selection of daclatasvir or ledipasvir and the use of ribavirin were at the discretion of the treating physician; most patients (94.4%) had ribavirin in their regimen. Among patients treated with sofosbuvir plus ribavirin for 12 weeks, the SVR rates were 86% for those who received ledipasvir (n=164) and 82% for those who received daclatasvir (n=82).

Based on these limited data, consideration should be given to the addition of ribavirin when working with more difficult-to-treat patients, such as those with compensated cirrhosis. Due to the complexity of accessing this regimen (a combination of 2 different manufacturer's products), this is recommended as an alternative regimen.

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 1b Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: **Peginterferon/Ribavirin-Experienced, Genotype 1b Patients With Compensated Cirrhosis**[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, B
ALTERNATIVE	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) with dasabuvir (600 mg) as part of an extended-release regimen or plus twice-daily dosed dasabuvir (250 mg)[c]	12 weeks	I, A

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Please see statement on FDA warning regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis.

Recommended Regimens

Elbasvir/Grazoprevir

The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) was evaluated in patients with a history of failed peginterferon/ribavirin therapy in the C-EDGE TE study. In this phase 3 trial, patients were randomized to 12 weeks or 16 weeks of elbasvir/grazoprevir, with or without ribavirin. Genotype 1-infected patients treated for 12 weeks without ribavirin had an overall SVR rate of 93.8% (90/96), which was nearly identical to the response rate in patients treated for 12 weeks with added ribavirin (94.4%, 84/89) (Kwo, 2017). Response rates were similar in the 16-week arms without ribavirin (94.8%, 91/96) and with ribavirin (96.9%, 93/96). A subset analysis of patients with compensated cirrhosis revealed similar response rates to the population without cirrhosis when treated with elbasvir/grazoprevir without ribavirin for 12 weeks (SVR with cirrhosis 95% [19/20]; SVR without cirrhosis 94.9% [37/39]).

The presence of certain baseline NS5A RASs appears to be the single best predictor of relapse with the 12-week

elbasvir/grazoprevir regimen. In genotype 1a-infected patients treated with elbasvir/grazoprevir, decreased efficacy was seen among those with baseline NS5A RASs when assessed by population sequencing (25% limit of detection). These RASs included substitutions at positions M28, Q30, L31, H58, and Y93. Among 21 genotype 1a-infected patients with baseline NS5A RASs (>5 fold), only 52.4% (11/21) achieved SVR due to a higher relapse rate (Kwo, 2015).

A subsequent integrated analysis of phase 2 and phase 3 trials confirmed a lower SVR rate in treatment-experienced, genotype 1a-infected patients with these specific baseline NS5A RASs (90%, 167/185) versus patients without baseline RASs (99%, 390/393) (Zeuzem, 2017). In patients treated with 12 weeks of elbasvir/grazoprevir without ribavirin, 64% (9/14) with baseline elbasvir NS5A RASs achieved SVR compared to 96% (52/54) among those without baseline RASs. Extension of therapy to 16 weeks or 18 weeks with the addition of weight-based ribavirin increased the response rate to 100% regardless of the presence of baseline NS5A RASs, suggesting this approach can overcome the negative impact of NS5A RASs seen with the 12-week regimen (Jacobson, 2015b).

Based on the known inferior response in patients with specific NS5A RASs, NS5A resistance testing is recommended in genotype 1a-infected patients being considered for elbasvir/grazoprevir therapy. If these RASs are present, treatment extension to 16 weeks with the addition of weight-based ribavirin (1000 mg [<75 kg] to 1200 mg [≥75 kg]) is recommended to decrease relapse risk. Lack of access to RAS testing or results should not be used as a means to limit access to HCV therapy.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive and -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with sofosbuvir (400 mg)/velpatasvir (100 mg) as a daily fixed-dose combination for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1-infected, treatment-experienced patients was 99% (109/110), with 100% (78/78) in participants with genotype 1a infection and 97% (31/32) in those with genotype 1b infection. Among patients previously treated with peginterferon/ribavirin, 98% (50/51) achieved SVR; 100% (48/48) of those previously treated with a DAA plus peginterferon/ribavirin achieved SVR. The single treatment-experienced patient who did not respond to this regimen was a genotype 1b-infected, black adult with cirrhosis and IL28 TT genotype. This individual had a persistently detectable HCV viral load during previous peginterferon/ribavirin therapy. This regimen was well tolerated and there was no significant difference in the rate of adverse events in the sofosbuvir/velpatasvir group (78%) versus the placebo group (77%).

Glecaprevir/Pibrentasvir

The EXPEDITION-1 trial investigated use of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks in 146 patients with compensated cirrhosis infected with genotype 1, 2, 4, 5, or 6. Twenty-five percent (36/146) of enrolled patients were non-DAA treatment experienced. SVR12 was 98.9% (89/90) among genotype1-infected patients. The single treatment failure occurred in a patient with genotype 1a infection who relapsed at post-treatment week 8 (Forns, 2017). Ninety-one percent of patients (133/146) had a Child-Pugh score of 5 and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count <100 x 10^9/L and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. Glecaprevir/pibrentasvir is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

Alternative Regimens

Ledipasvir/Sofosbuvir + Ribavirin

The double-blind, placebo-controlled, phase 2 SIRIUS trial enrolled genotype 1-infected patients with compensated cirrhosis who did not achieve SVR with peginterferon/ribavirin plus telaprevir or boceprevir. Participants were randomized

to either 12 weeks of placebo followed by 12 weeks of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus ribavirin, or ledipasvir/sofosbuvir plus placebo for 24 weeks. The SVR rates were similar in the study arms: 96% (74/77) in the group that received ledipasvir/sofosbuvir plus ribavirin for 12 weeks (3 relapses), and 97% (75/77) in the group that received ledipasvir/sofosbuvir for 24 weeks (2 relapses) (Bourliere, 2015).

These findings are further supported by a post hoc analysis of treatment-naive or -experienced, genotype 1-infected patients with compensated cirrhosis who were treated with ledipasvir/sofosbuvir in phase 2 and phase 3 studies (including the SIRIUS trial). In this analysis, ledipasvir/sofosbuvir for 12 weeks was inferior to ledipasvir/sofosbuvir plus ribavirin for 12 weeks. Safety and tolerability were similar in the groups and, apart from anemia, reported adverse events did not differ substantially between patients treated with or without ribavirin (Reddy, 2015). Due to the need for ribavirin, this regimen is recommended as an alternative for genotype 1-infected patients with a history of peginterferon/ribavirin failure who have compensated cirrhosis.

Baseline NS5A RASs adversely impact response to ledipasvir/sofosbuvir therapy. The magnitude of impact varies based on several factors, including virus (genotype subtype, specific RAS); regimen (companion drugs, use of ribavirin); and patient factors (treatment experience, presence of cirrhosis). In an analysis of more than 350 genotype 1-infected, treatment-experienced patients with cirrhosis, the presence of baseline ledipasvir RASs (defined as RASs resulting in a >2.5-fold shift in ledipasvir EC_{50}) detected at a 1% level resulted in a lower SVR12 rate compared to those without baseline RASs (Zeuzem, 2017). The SVR12 rates were 89% with RASs versus 96% in the absence of RASs with a 12-week course of ledipasvir/sofosbuvir plus ribavirin, and 87% versus 100%, respectively, with a 24-week course of ledipasvir/sofosbuvir without ribavirin. The impact of baseline RASs is likely greater in a genotype 1a only population.

Given the vulnerable nature of this population, baseline NS5A resistance testing should be considered for genotype 1a-infected, treatment-experienced patients with compensated cirrhosis prior to use of ledipasvir/sofosbuvir. If ledipasvir-associated RASs are detected, a different regimen should be used to optimize treatment response.

Paritaprevir/Ritonavir/Ombitasvir + Dasabuvir

The TURQUOISE-III study evaluated the safety and efficacy of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus twice-daily dosed dasabuvir (250 mg) without ribavirin for 12 weeks in patients with genotype 1b infection and compensated cirrhosis. Sixty patients were enrolled (62% men; 55% treatment experienced; 83% with the IL28B non-CC genotype; 22% with a platelet count <90 x 10^9/L; and 17% with an albumin level <3.5 g/dL). All patients completed treatment and achieved SVR12 (Feld, 2016). Based on this study, treating patients with genotype 1b infection with paritaprevir/ritonavir/ombitasvir plus dasabuvir without ribavirin is ranked as an alternative regimen (primarily because of drug interactions), regardless of prior treatment experience or the presence of compensated cirrhosis.

The US Food and Drug Administration (FDA) released a warning in October 2015 regarding the use of paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with cirrhosis. (This statement is based on our review of the limited data available from the FDA and will be updated if and when more data become available.) Paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with Child-Turcotte-Pugh (CTP) class B or class C hepatic impairment (decompensated liver disease). The manufacturer's pharmacovigilance program reported the rapid onset of liver injury and, in some cases, hepatic decompensation in patients with cirrhosis—including CTP class A compensated cirrhosis and decompensated cirrhosis—who were receiving paritaprevir/ritonavir/ombitasvir ± dasabuvir. The liver injury and decompensating events occurred largely during the first 4 weeks of therapy and primarily involved a rapid increase in total and direct bilirubin, often associated with a concomitant increase in liver enzyme levels. In most cases, early recognition and prompt discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir resulted in resolution of the hepatic injury. However, some patients (including at least 2 persons with CTP class A compensated cirrhosis) died or required liver transplantation. Although cirrhosis carries a 2% to 4% annual risk of hepatic decompensation, the rapid onset of hepatic decompensation and, in many cases, its resolution with discontinuation of paritaprevir/ritonavir/ombitasvir ± dasabuvir suggest drug-induced liver injury. Although paritaprevir/ritonavir/ombitasvir ± dasabuvir is contraindicated in patients with CTP class B or class C cirrhosis and decompensated liver disease, predictors of these events in patients with CTP class A cirrhosis are currently unclear.

For patients with CTP class A cirrhosis, the unlikely but real possibility of drug-induced liver injury should be discussed with the patient. If the decision is made to initiate treatment with paritaprevir/ritonavir/ombitasvir ± dasabuvir, close monitoring of total and direct bilirubin and transaminase levels every 1 to 2 weeks for the first 4 weeks of therapy is recommended to ensure early detection of drug-induced liver injury. Educating patients about the importance of reporting systemic symptoms, such as jaundice, weakness, and fatigue, is also strongly recommended. The regimen should be discontinued immediately if drug-induced liver injury is suspected. If a patient is already taking paritaprevir/ritonavir/ombitasvir ± dasabuvir and tolerating the regimen, laboratory monitoring as noted without discontinuation of treatment is recommended unless there are signs or symptoms of liver injury. If heightened monitoring cannot be provided during the first 4 weeks of therapy with paritaprevir/ritonavir/ombitasvir ± dasabuvir in patients with compensated cirrhosis, use of these regimens is not recommended.

Last update: September 21, 2017

NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

NS3 Protease Inhibitor (Telaprevir, Boceprevir, or Simeprevir) + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for all genotype 1b patients, and genotype 1a patients without baseline NS5A RASs[b] for elbasvir	12 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for genotype 1a patients with baseline NS5A RASs[b] for elbasvir	16 weeks	IIa, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

Recommended Regimens

Ledipasvir/Sofosbuvir

The ION-2 trial evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in genotype 1-infected patients in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus peginterferon/ribavirin failed (Afdhal, 2014b). SVR12 rates with the 12-week and 24-week ledipasvir/sofosbuvir regimens were 94% and 98%, respectively. Relapse rates were numerically higher with the 12-week regimen versus the 24-week regimen. The presence of cirrhosis and/or baseline NS5A RASs were the major reasons for the higher relapse rate in the 12-week study arm. Thus, genotype 1-infected patients without cirrhosis in whom a prior regimen of peginterferon/ribavirin plus an HCV protease inhibitor failed can receive a 12-week course of ledipasvir/sofosbuvir.

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (Feld, 2015). In this study, 100% (48/48) of participants who previously experienced treatment failure with a protease inhibitor plus peginterferon/ribavirin achieved SVR12 (Feld, 2015). These data are supported by similarly high SVR rates seen in a preceding phase 2, open-label trial wherein 100% (27/27) of patients with the same type of treatment failure history achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir therapy (Pianko, 2015).

Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 genotype 1-infected patients had been previously treated with either an NS5A inhibitor or a protease inhibitor. Twenty-four percent of these patients had cirrhosis. Among those previously treated with protease inhibitor-based therapy (which includes simeprevir, boceprevir or telaprevir without NS5A inhibitor exposure) who were retreated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks, 92% (23/25) achieved SVR12. Simeprevir plus sofosbuvir failures were included. Of the 2 patients who did not achieve SVR, neither experienced virologic failure (Poordad, 2017); (Poordad, 2017b).

Alternative Regimens

Elbasvir/Grazoprevir + Ribavirin

Grazoprevir is a next-generation HCV NS3/4A protease inhibitor that retains activity in vitro against many common protease inhibitor resistant substitutions (Summa, 2012); (Howe, 2014). Elbasvir is an HCV NS5A inhibitor. The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with expanded weight-based ribavirin (800 mg to 1400 mg) was evaluated in an open-label, phase 2 study of 79 patients who experienced prior treatment failure with interferon-based therapy plus a protease inhibitor (Forns, 2015a). Most enrolled participants had a prior treatment failure with peginterferon/ribavirin plus either boceprevir (35%, n=28) or telaprevir (54%, n=43). Importantly, 83% of enrolled patients had experienced virologic failure with their prior protease inhibitor-containing regimen and 44% had detectable NS3 RASs to early-generation protease inhibitors at study entry. SVR12 was attained in 96% of patients, including in 93% (28/30) of genotype 1a-infected patients and 94% (32/34) in those with cirrhosis. Baseline NS3 RASs did not appear to have a large impact on treatment response with an SVR12 rate of 91% (31/34). Presence of NS5A or dual NS3/NS5A substitutions was associated with lower SVR12 rates of 75% and 66%, respectively. But with only 3 failures in the entire study, firm conclusions cannot be drawn.

Consistent with recommendations for other populations, a 12-week course of elbasvir/grazoprevir is a recommended regimen for patients with genotype 1a infection and no baseline NS5A RASs. Extension of therapy to 16 weeks plus weight-based ribavirin is an alternative treatment option for genotype 1a-infected patients with baseline NS5A RASs resulting in a >5-fold shift in elbasvir potency.

Last update: September 21, 2017

NS3 Protease Inhibitor + Peginterferon/Ribavirin-Experienced, Genotype 1 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

NS3 Protease Inhibitor (Telaprevir, Boceprevir, or Simeprevir) + Peginterferon/Ribavirin Treatment-Experienced, Genotype 1 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for all genotype 1b patients, and genotype 1a patients without baseline NS5A RASs[c] for elbasvir	12 weeks	IIa, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for genotype 1a patients with baseline NS5A RASs[c] for elbasvir	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] Includes genotype 1a resistance-associated substitutions at amino acid positions 28, 30, 31, or 93 known to confer antiviral resistance.

Recommended Regimens

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (Feld, 2015). Patients in the placebo arm were eligible to roll over into a deferred therapy arm with the same regimen. The overall response rate among genotype 1-infected, treatment-experienced patients was 99.1% (109/110), with 100% (78/78) in patients with genotype 1a infection and 96.9% (31/32) among those with genotype 1b infection. In this study,

100% (48/48) of participants who previously experienced treatment failure with a protease inhibitor plus peginterferon/ribavirin achieved SVR12 (Feld, 2015). These data are supported by similarly high SVR rates seen in a preceding phase 2, open-label trial wherein 100% (27/27) of patients with the same type of treatment failure history achieved SVR12 with 12 weeks of sofosbuvir/velpatasvir therapy (Pianko, 2015).

Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 genotype 1-infected patients had been previously treated with either an NS5A inhibitor or a protease inhibitor. Twenty-four percent of these patients had cirrhosis. Among those previously treated with NS3/4A protease inhibitor-based therapy (which includes simeprevir, boceprevir or telaprevir without NS5A inhibitor exposure) who were retreated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks, 92% (23/25) achieved SVR12. Simeprevir plus sofosbuvir failures were included. Of the 2 patients who did not achieve SVR, neither experienced virologic failure (Poordad, 2017); (Poordad, 2017b).

Alternative Regimens

Ledipasvir/Sofosbuvir + Ribavirin

The ION-2 trial evaluated the safety and efficacy of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in genotype 1-infected patients in whom prior treatment with an HCV protease inhibitor (telaprevir or boceprevir) plus peginterferon/ribavirin failed (Afdhal, 2014b). SVR12 with 12 weeks of therapy was 94%. Relapse rates were numerically higher in the 12-week treatment arms than in the 24-week arms. The pretreatment presence of cirrhosis and/or NS5A RASs were the major reasons for the higher relapse rate in the 12-week arm. Thus, genotype 1-infected patients without cirrhosis in whom a prior regimen of peginterferon/ribavirin plus an HCV protease inhibitor failed should receive ledipasvir/sofosbuvir plus weight-based ribavirin for 12 weeks to optimize treatment response (Bourliere, 2015). Due to the need for ribavirin, this is recommended as an alternative regimen.

Elbasvir/Grazoprevir + Ribavirin

Grazoprevir is a next-generation HCV NS3/4A protease inhibitor that retains activity in vitro against many common protease inhibitor RASs (Summa, 2012); (Howe, 2014). Elbasvir is an HCV NS5A inhibitor. The daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) with expanded weight-based ribavirin (800 mg to 1400 mg) was evaluated in an open-label, phase 2 study of 79 patients who experienced a prior treatment failure with interferon-based therapy plus a protease inhibitor (Forns, 2015a). Most enrolled participants had a prior treatment failure with peginterferon/ribavirin plus either boceprevir (35%, n=28) or telaprevir (54%, n=43). Importantly, 83% of enrolled patients had experienced virologic failure with their prior protease inhibitor-containing regimen and 44% had detectable NS3 RASs to early-generation protease inhibitors at study entry. SVR12 was attained in 96% of patients, including 93% (28/30) of genotype 1a-infected patients and 94% (32/34) of those with cirrhosis. Baseline NS3 RASs did not appear to have a large impact on treatment response with an SVR12 rate of 91% (31/34). Presence of NS5A or dual NS3/NS5A substitutions was associated with lower SVR12 rates of 75% and 66%, respectively. But with only 3 failures in the entire study, firm conclusions cannot be drawn.

Consistent with recommendations for other populations, extension of therapy to 16 weeks with ribavirin is recommended for patients with baseline NS5A RASs resulting in a >5-fold shift in elbasvir potency. Due to the need for ribavirin, both the 12-week and 16-week course of therapy are recommended as alternative regimens.

Last update: September 21, 2017

Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) for genotype 1a patients	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a], regardless of subtype	12 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for genotype 1b patients	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) plus weight-based ribavirin, except in simeprevir failures	12 weeks	IIa, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Sofosbuvir/Velpatasvir/Voxilaprevir

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of daily fixed-dose sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) to 12 weeks of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced patients (Bourliere, 2017). Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. SVR12 rates for patients with genotype 1 infection were 97% (76/78) for sofosbuvir/velpatasvir/voxilaprevir and 90% (60/66) for sofosbuvir/velpatasvir. Only sofosbuvir/velpatasvir/voxilaprevir met the prespecified efficacy (SVR12) threshold of 85%. There was 1 relapse in the sofosbuvir/velpatasvir/voxilaprevir arm compared to 15 virologic failures (14 relapses, 1 virologic breakthrough) in the sofosbuvir/velpatasvir group. The single patient who experienced relapse in the sofosbuvir/velpatasvir/voxilaprevir arm did not have treatment-emergent RASs; 9 of the patients with relapse in the sofosbuvir/velpatasvir arm developed NS5A treatment-emergent RASs. This study supports sofosbuvir/velpatasvir/voxilaprevir as a recommended regimen for the treatment of patients with a history of treatment failure using a non-NS5A inhibitor sofosbuvir-containing DAA regimen.

Glecaprevir/Pibrentasvir

There are limited data to guide recommendations for the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for patients with genotype 1a or 1b infection and a prior treatment failure with a sofosbuvir-containing DAA regimen. In the phase 3, open-label ENDURANCE-1 study, 351 and 352 patients received 8 weeks or 12 weeks of glecaprevir/pibrentasvir, respectively (Zeuzem, 2016). All patients had genotype 1 infection and were noncirrhotic; 38% of patients in each study arm were treatment experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). However, only 1 patient in the 8-week arm and 2 patients in the 12-week arm had a history of treatment failure with a sofosbuvir-containing regimen.

In the EXPEDITION-1 study, 146 patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis were treated with 12 weeks of glecaprevir/pibrentasvir. Twenty-five of these patients were treatment experienced; only 11 had a previous treatment failure with a sofosbuvir-containing regimen (Forns, 2017). None of these patients had a prior simeprevir plus sofosbuvir regimen failure. However, 12 weeks of glecaprevir/pibrentasvir was evaluated in prior NS3/4A treatment failures in the MAGELLAN-1 trial, which included patients with prior simeprevir plus sofosbuvir treatment failure (Poordad, 2017); (Poordad, 2017b).

With the limited clinical trial experience with glecaprevir/pibrentasvir in patients with a history of sofosbuvir-containing regimen treatment failure coming primarily from a 12-week duration of therapy, we recommend 12 weeks of therapy in this patient population until there are further clinical trial or real-world data to support a shorter treatment duration.

Sofosbuvir/Velpatasvir

As described in the discussion of sofosbuvir/velpatasvir/voxilaprevir, the POLARIS-4 trial included a 12-week arm of the fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in non-NS5A inhibitor-DAA experienced patients (Bourliere, 2017). While only sofosbuvir/velpatasvir/voxilaprevir met the overall prespecified efficacy (SVR12) threshold of 85%, this was primarily driven by treatment failure in patients with genotype 1a or 3 infection. Forty-four patients with genotype 1a infection, 22 with genotype 1b infection, 33 with genotype 2 infection, and 52 with genotype 3 infection were included in the sofosbuvir/velpatasvir arm. Overall, there were 15 virologic failures (14 relapses); 5 were in genotype 1a-infected patients and 8 were in those with genotype 3 infection. One genotype 1b-infected patient and a single genotype 2-infected patient also experienced treatment failure. Although this study was not powered to assess differences in efficacy by genotype/subtype, the SVR12 rates in genotype 1b-infected patients were 95% and 96% for sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, respectively. There were fewer genotype 1b-infected patients who experienced a previous treatment failure specifically with a non-NS5A inhibitor sofosbuvir-containing regimen (n=12), and no virologic failures.

Alternative Regimen

Ledipasvir/Sofosbuvir + Ribavirin

Retreatment with the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg) in patients with genotype 1 infection, with or without cirrhosis, in whom a sofosbuvir-containing (excluding simeprevir) regimen failed was evaluated in 2 small pilot studies utilizing ledipasvir/sofosbuvir for 12 weeks. Among patients with a prior treatment failure with 24 weeks of sofosbuvir plus ribavirin, high SVR rates were noted when patients were retreated with ledipasvir/sofosbuvir for 12 weeks (Osinusi, 2014). Ledipasvir/sofosbuvir plus ribavirin has also been evaluated in patients in whom prior treatment with sofosbuvir plus peginterferon/ribavirin or sofosbuvir and ribavirin failed. In a study of 51 patients, retreatment with ledipasvir/sofosbuvir plus ribavirin for 12 weeks led to SVR12 in 100% of 50 patients with genotype 1 infection. One virologic failure was observed in a patient determined to have genotype 3 infection prior to retreatment (Wyles, 2015b).

Last update: September 21, 2017

Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients With Compensated Cirrhosis

Recommended regimens listed by evidence level and alphabetically for:

Non-NS5A Inhibitor, Sofosbuvir-Containing Regimen-Experienced, Genotype 1 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) for genotype 1a patients	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b], regardless of subtype	12 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for genotype 1b patients	12 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Sofosbuvir/Velpatasvir/Voxilaprevir

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) to 12 weeks of sofosbuvir/velpatasvir in non-NS5A inhibitor DAA-experienced patients (Bourliere, 2017). Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. SVR12 rates for patients with genotype 1 infection were 97% (76/78) for sofosbuvir/velpatasvir/voxilaprevir and 90% (60/66) for sofosbuvir/velpatasvir. Only sofosbuvir/velpatasvir/voxilaprevir met the prespecified efficacy (SVR12) threshold of 85%. The vast majority of patients had experienced prior treatment failure with a sofosbuvir plus simeprevir regimen. Overall, there was 1 relapse in the sofosbuvir/velpatasvir/voxilaprevir arm compared to 15 virologic failures (14 relapses, 1 virologic breakthrough) in the sofosbuvir/velpatasvir group. The single patient who experienced relapse in the sofosbuvir/velpatasvir/voxilaprevir arm did not have treatment-emergent RASs; 9 of the patients with relapse in the sofosbuvir/velpatasvir arm developed NS5A treatment-emergent RASs. This study supports sofosbuvir/velpatasvir/voxilaprevir as a recommended regimen for the treatment of patients with a history of treatment failure with a sofosbuvir-containing DAA regimen, regardless of the presence of cirrhosis.

Glecaprevir/Pibrentasvir

In the EXPEDITION-1 study, 146 patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis were treated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 12 weeks (Forns, 2017). Of these patients, 25 patients were previously treated with interferon or peginterferon ± ribavirin and 11 were previously treated with sofosbuvir and ribavirin ± peginterferon. Overall, 99% (145/146) of patients achieved SVR 12. The single patient who did not respond to therapy had genotype 1a infection and relapsed at post-treatment week 8. None of the patients enrolled in the EXPEDITION-1 trial were previously treated with simeprevir plus sofosbuvir. However, 12 weeks of glecaprevir/pibrentasvir was evaluated in patients with NS3/4A treatment failure in the MAGELLAN-1 trial, which included simeprevir plus sofosbuvir treatment failures (Poordad, 2017); (Poordad, 2017b).

Sofosbuvir/Velpatasvir

As described in the discussion of sofosbuvir/velpatasvir/voxilaprevir, the POLARIS-4 trial included a 12-week arm of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in non-NS5A inhibitor DAA-experienced patients (Bourliere, 2017). While only sofosbuvir/velpatasvir/voxilaprevir met the overall prespecified efficacy (SVR12) threshold of 85%, this was primarily driven by treatment failure in patients with genotype 1a or 3 infection. Forty-four patients with genotype 1a infection, 22 with genotype 1b infection, 33 with genotype 2 infection, and 52 with genotype 3 infection were included in the sofosbuvir/velpatasvir arm. Overall, there were 15 virologic failures (14 relapses); 5 were in genotype 1a-infected patients and 8 were in those with genotype 3 infection, and most of these patients had cirrhosis. One genotype 1b-infected patient and a single genotype 2-infected patient also experienced treatment failure. Although this study was not powered to assess differences in efficacy by genotype/subtype, the SVR12 rates in genotype 1b-infected patients were 95% and 96% for sofosbuvir/velpatasvir and sofosbuvir/velpatasvir/voxilaprevir, respectively. There were fewer genotype 1b-infected patients who had specifically experienced a prior non-NS5A inhibitor sofosbuvir-containing regimen failure (n=12), and no virologic failures.

Last update: September 21, 2017

NS5A Inhibitor DAA-Experienced Genotype 1 Patients

Recommended and alternative regimens for:

NS5A Inhibitor DAA-Experienced, Genotype 1 Patients With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg)	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b] except NS3/4 protease inhibitor inclusive DAA combination regimens	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimen

Sofosbuvir/Velpatasvir/Voxilaprevir

The placebo-controlled, phase 3 POLARIS-1 trial evaluated a 12-week course of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100mg) in patients with a prior NS5A inhibitor-containing DAA regimen. The majority (61%) experienced a failure with a combination regimen of an NS5B inhibitor plus an NS5A inhibitor, such as sofosbuvir/ledipasvir (Bourliere, 2017). The overall SVR12 rate was 97% (146/150) in genotype 1-infected patients. SVR12 rates were 96% (97/101) for participants with genotype 1a infection and 100% (45/45) for those with genotype 1b infection. A single genotype 1-infected patient experienced relapse; this individual had subtype 1a infection and cirrhosis. Baseline RASs and the presence of cirrhosis were not significant predictors of virologic failure in genotype 1 infection. Serious adverse events were similar between the placebo and treatment arms; only 1 patient discontinued therapy due to an adverse event. Headache, diarrhea, and nausea were more common in those patients receiving sofosbuvir/velpatasvir/voxilaprevir compared to placebo.

Alternative Regimen

Glecaprevir/Pibrentasvir

In parts 1 and 2 of the MAGELLAN-1 trial, 42 genotype 1-infected patients had previously been treated with either an NS5A inhibitor or an NS3/4A protease inhibitor (Poordad, 2017); (Poordad, 2017b). Twenty-four percent of these patients had cirrhosis and 79% were genotype 1a infected. Patients who were previously treated with an NS5A inhibitor (ledipasvir or daclatasvir) and not concomitantly treated with a NS3/4A protease inhibitor were retreated with the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination

pills for 16 weeks. Among these patients, 94% (16/17) achieved SVR 12. The single patient who did not respond to therapy had an on-treatment virologic failure. Due to the 16-week duration of therapy and limited supporting data, this is recommended as an alternative regimen.

Last update: September 21, 2017

Treatment-Experienced Genotype 2

The following pages include guidance for management of treatment-experienced patients with genotype 2 infection.

- Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis
- Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis
- Sofosbuvir + Ribavirin-Experienced, Genotype 2 Patients With or Without Compensated Cirrhosis

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for: **Peginterferon/Ribavirin-Experienced, Genotype 2 Patients Without Cirrhosis**		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, A
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
ALTERNATIVE	DURATION	RATING
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)	12 weeks	IIa, B

[a] This is a 3-tablet coformulation. Please refer to the prescribing information.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 4 trial was a single-arm study of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills for 8 weeks in patients with genotype 2, 4, 5, or 6 infection without cirrhosis who were treatment-naive or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) (Hassanein, 2016). One hundred forty-five genotype 2-infected patients were enrolled with a 98% SVR12. Two patients experienced relapse; both were treatment experienced.

Sofosbuvir/Velpatasvir

In the randomized, open-label ASTRAL-2 study, genotype 2-infected patients were treated with 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) or sofosbuvir plus ribavirin (Foster, 2015a). Of the 266 participants, a minority (15%) had a history of previous peginterferon/ribavirin treatment failure and a similar proportion (14%) had compensated cirrhosis. Overall, the combination of sofosbuvir/velpatasvir yielded a statistically significant superior SVR12 rate of 99% vs 94% for sofosbuvir plus ribavirin. The only treatment failure in the sofosbuvir/velpatasvir arm was a patient who withdrew from the study after a single day due to side effects (anxiety). In contrast, there were 6 virologic failures in the sofosbuvir plus ribavirin arm. Fatigue and anemia were more commonly reported in patients receiving sofosbuvir plus ribavirin.

The phase 3 POLARIS-2 study randomized patients to 8 weeks of the fixed-dose combination of sofosbuvir/velpatasvir/voxilaprevir versus 12 weeks of sofosbuvir/velpatasvir. Fifty-three genotype 2-infected patients were in the sofosbuvir/velpatasvir arm and all achieved SVR (100%, 53/53) (Jacobson, 2017). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection, including those with a past peginterferon/ribavirin treatment failure and patients with compensated cirrhosis.

Alternative Regimen

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks to 24 weeks has been shown to have efficacy in genotype 2 infection. However, available data in patients previously treated with peginterferon/ribavirin are very limited (Wyles, 2015); (Sulkowski, 2014a). For patients who require treatment and are unable to access sofosbuvir/velpatasvir, treatment with daclatasvir/sofosbuvir for 12 weeks is an alternative regimen with consideration of extension of therapy to 24 weeks in more difficult-to-treat patients, such as those with cirrhosis.

Last update: September 21, 2017

Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 2 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	I, B
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg)[c] plus sofosbuvir (400 mg)	16 to 24 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.
[c] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.

Recommended Regimens

Sofosbuvir/Velpatasvir

In the randomized, open-label ASTRAL-2 study, genotype 2-infected patients were treated with 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) or sofosbuvir plus ribavirin (Foster, 2015a). Of the 266 participants, a minority (15%) had a history of previous peginterferon/ribavirin treatment failure and a similar proportion (14%) had compensated cirrhosis. Overall, the combination of sofosbuvir/velpatasvir yielded a statistically significant superior SVR12 rate of 99% vs 94% for sofosbuvir plus ribavirin. The only treatment failure in the sofosbuvir/velpatasvir arm was a patient who withdrew from the study after a single day due to side effects (anxiety). In contrast, there were 6 virologic failures in the sofosbuvir plus ribavirin arm. Fatigue and anemia were more commonly reported in patients receiving sofosbuvir plus ribavirin.

The phase 3 POLARIS-2 study randomized patients to 8 weeks of sofosbuvir/velpatasvir/voxilaprevir or 12 weeks of sofosbuvir/velpatasvir. Fifty-three genotype 2-infected patients were included in the sofosbuvir/velpatasvir arm and all achieved SVR (100%, 53/53) (Jacobson, 2017). This study confirms the high efficacy and safety of this 12-week regimen in patients with genotype 2 infection, including those with a past peginterferon/ribavirin treatment failure and patients with compensated cirrhosis.

Considering the high SVR12 rate and fewer side effects with sofosbuvir/velpatasvir, regimens with peginterferon and/or

ribavirin are no longer recommended for genotype 2 infection.

Glecaprevir/Pibrentasvir

The phase 3, single arm, open-label EXPEDITION-1 study investigated the safety and efficacy of a 12-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis (Forns, 2017). Treatment-naive and -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) were included in the trial. Overall, only 25% (n=36) of patients were treatment experienced. The SVR12 in the genotype 2-infected patients was 100% (31/31). Overall, 91% percent (133/146) of patients had a Child-Pugh score of 5, and 9% (13/146) had a Child-Pugh score of 6. Twenty percent of patients had a platelet count <100 x 10^9/L and all but 1 participant had a normal albumin level. In this patient population with compensated cirrhosis, the regimen was safe and well tolerated. There were 11 serious adverse events; none were DAA-related and no adverse events led to discontinuation of the study drugs. This is a safe and highly efficacious 12-week regimen in patients with well-compensated cirrhosis.

Alternative Regimen

Daclatasvir + Sofosbuvir

Daclatasvir (60 mg) plus sofosbuvir (400 mg) for 12 weeks to 24 weeks has been shown to have efficacy in genotype 2 infection. However, available data in patients previously treated with peginterferon/ribavirin are very limited (Wyles, 2015); (Sulkowski, 2014a). For patients who require treatment and are unable to access sofosbuvir/velpatasvir, treatment with daclatasvir/sofosbuvir for 12 weeks is an alternative regimen with consideration of extension of therapy to 24 weeks in more difficult-to-treat patients, such as those with cirrhosis.

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Sofosbuvir + Ribavirin-Experienced, Genotype 2 Patients With or Without Compensated Cirrhosis

Recommended regimens listed by evidence level for:

Sofosbuvir + Ribavirin-Experienced, Genotype 2 Patients With or Without Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	12 weeks	IIb, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Sofosbuvir/Velpatasvir

The phase 3, open-label, randomized clinical trial POLARIS-4 compared a 12-week course of sofosbuvir/velpatasvir/voxilaprevir to 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) in non-NS5A inhibitor DAA-experienced patients (Bourliere, 2017). Overall, 69% of patients were previously exposed to sofosbuvir plus ribavirin ± peginterferon, and 11% were exposed to sofosbuvir plus simeprevir. Cirrhosis was common, 46% in both study arms. Among patients with genotype 2 infection, 97% (32/33) who received 12 weeks of sofosbuvir/velpatasvir achieved SVR12. Overall for the study, the sofosbuvir/velpatasvir arm did not meet the prespecified performance goal of > 85% efficacy (prespecified p value 0.025). However, this was primarily driven by treatment failure in patients with genotype 3 or 1a infection. The single genotype 2-infected patient who experienced virologic failure in the sofosbuvir/velpatasvir arm had virologic breakthrough rather than relapse and was the only patient with an NS5B RAS at any time point. The S292T substitution emerged at the time of virologic failure. Diarrhea and nausea were more commonly reported in the sofosbuvir/velpatasvir/voxilaprevir group.

Glecaprevir/Pibrentasvir

The phase 3, randomized, double-blind, placebo-controlled ENDURANCE-2 study enrolled treatment-naive or -experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) genotype 2-infected patients without cirrhosis. Participants were treated with 12 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills or placebo (Kowdley, 2016b). Among 202 patients in the glecaprevir/pibrentasvir arm, 30% (61/202) were treatment experienced, of whom 6 had previously received sofosbuvir plus ribavirin ± peginterferon. The overall SVR12 in the intention-to-treat analysis was 99%, and SVR12 was achieved in all 6 patients with a prior sofosbuvir-based treatment failure. The most common adverse events in the glecaprevir/pibrentasvir arm were headache and fatigue.

The phase 3, single arm, open-label EXPEDITION-1 study investigated the safety and efficacy of a 12-week course of

glecaprevir/pibrentasvir in patients with genotype 1, 2, 4, 5, or 6 infection and compensated cirrhosis. Treatment-naive and -experienced patients (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon) were included in the trial. Overall, only 25% (n=36) of patients were treatment experienced, 11 of which had a history of sofosbuvir failure (although it is unclear how many of these patients had genotype 2 infection). The SVR12 in the genotype 2-infected patients was 100% (31/31) (Forns, 2017).

No sofosbuvir treatment failures were included in the SURVEYOR study, which investigated 8 weeks of therapy in patients with genotype 2 infection without cirrhosis. Thus, this regimen cannot be recommended in this patient population until supported by clinical data (Poordad, 2017).

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Treatment-Experienced Genotype 3

The following pages include guidance for management of treatment-experienced patients with genotype 3 infection.

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Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 3 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)[a]	12 weeks	I, A
ALTERNATIVE	**DURATION**	**RATING**
Daily daclatasvir (60 mg)[b] plus sofosbuvir (400 mg)[a]	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[c]	16 weeks	IIa, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) when Y93H is present	12 weeks	IIb, B

[a] Baseline RAS testing for Y93H is recommended. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.
[b] The dose of daclatasvir may need to be increased or decreased when used concomitantly with cytochrome P450 3A/4 inducers and inhibitors, respectively. Please refer to the prescribing information and the section on HIV/HCV coinfection for patients on antiretroviral therapy.
[c] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimen

Sofosbuvir/Velpatasvir

The phase 3 ASTRAL-3 study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (without ribavirin) in 277 genotype 3-infected patients, including 71 with prior treatment experience and 80 with compensated cirrhosis (Foster, 2015a). Despite a high combined SVR12 rate of 95% (264/277), both prior treatment (90% SVR) and compensated cirrhosis (91% SVR) had a moderate negative impact on treatment response. The addition of ribavirin appeared to increase SVR12 rates in a phase 2 study that included treatment-experienced, genotype 3-infected patients treated for 12 weeks with sofosbuvir (400 mg) plus 25 mg or 100 mg of velpatasvir, with or without ribavirin (Pianko, 2015).

The phase 3 POLARIS-2 study evaluated 12 weeks of sofosbuvir/velpatasvir versus 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in patients (any genotype) who were either treatment naive or had a previous peginterferon/ribavirin treatment failure. Eighty-nine genotype 3-infected patients (all without cirrhosis) received the sofosbuvir/velpatasvir regimen and 97% (86/89) achieved SVR12 (Jacobson, 2017). There were no virologic failures. These findings confirm the efficacy of this 12-week regimen in genotype 3-infected patients without cirrhosis.

Baseline NS5A substitutions in genotype 3 infection impact DAA treatment response, with the Y93H substitution having the greatest effect. In the ALLY-3 study, the Y93H substitution was detected at baseline in 9% (13/147) of participants (Nelson, 2015). SVR12 in these patients was 54% (7/13), including an SVR12 of 67% (6/9) in patients without cirrhosis. In the ASTRAL-3 study, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a).

Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced, genotype 3-infected patients without cirrhosis for whom sofosbuvir/velpatasvir is being considered. If the Y93H substitution is identified, a different regimen should be used, or weight-based ribavirin should be added as an alternative option.

Alternative Regimens

Daclatasvir + Sofosbuvir

The phase 3, open-label ALLY-3 study evaluated a 12-week course of daclatasvir (60 mg) plus sofosbuvir (400 mg) in treatment-naive or -experienced (interferon-based therapy or sofosbuvir plus ribavirin), genotype 3-infected patients without cirrhosis or with compensated cirrhosis. Treatment-experienced, genotype 3-infected patients without cirrhosis did well with an SVR12 rate of 94% (32/34) (Nelson, 2015).

Baseline NS5A substitutions in genotype 3 infection impact DAA treatment response, with the Y93H substitution having the greatest effect. In the ALLY-3 study, the Y93H substitution was detected at baseline in 9% (13/147) of patients (Nelson, 2015). The SVR12 in these patients was 54% (7/13), including an SVR12 of 67% (6/9) in patients without cirrhosis. In the ASTRAL-3 study, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a).

Pending additional data, baseline NS5A RAS testing is recommended in all treatment-experienced, genotype 3-infected patients without cirrhosis for whom daclatasvir plus sofosbuvir is being considered. If the Y93H substitution is identified, a different recommended regimen should be used, or weight-based ribavirin should be added as an alternative option.

Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 3 trial evaluated the safety and efficacy of a 12-week or 16-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in treatment-naive or -experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3-infected patients without cirrhosis or with compensated cirrhosis. Among the 44 treatment-experienced patients without cirrhosis, the SVR rates were 91% (20/22) and 96% (21/22) for 12 weeks and 16 weeks, respectively. All patients who experienced treatment failure had baseline RAS mutations. One patient in the 12-week study arm had an A30K RAS at baseline and a treatment-emergent Y93H RAS at failure resulting in the A30K+Y93H double RAS, which confers 69-fold resistance to glecaprevir/pibrentasvir. This was also true in the single relapse in the 16-week study arm. The second patient with relapse in the 12-week arm had a baseline Y93H RAS, which persisted at the time of failure. The Y93H substitution does not confer high-fold resistance to this regimen (Wyles, 2017a).

Based on these data, the appropriate length of therapy is unclear for genotype 3-infected, peginterferon/ribavirin-experienced patients. Until further data are available, a 16-week duration of treatment is recommended as an alternative option, especially if a baseline A30K substitution is present.

Sofosbuvir/Velpatasvir/Voxilaprevir

The efficacy of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in genotype 3 infection is supported by the phase 3 POLARIS trials, which investigated 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in DAA-naive patients and 12 weeks in DAA-experienced patients. The 8-week

regimen achieved noninferiority compared to a 12-week sofosbuvir/velpatasvir regimen in the POLARIS-3 study, which included 35 interferon-experienced patients with genotype 3 infection and cirrhosis (Jacobson, 2017). Thus, this regimen is recommended as an alternative option for patients with genotype 3 infection who have evidence of the Y93H RAS at baseline.

In the ASTRAL-3 study, which investigated 12 weeks of sofosbuvir/velpatasvir, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a). Due to the low number of patients with the Y93H mutation in the POLARIS-3 study and the difficult-to-treat nature of treatment-experienced, genotype 3-infected patients, we recommend 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to optimize SVR12.

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Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 3 Patients With Compensated Cirrhosis[a]

RECOMMENDED	DURATION	RATING
Daily fixed-dose elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir (400 mg)	12 weeks	I, B
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg)	12 weeks	IIb, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) plus weight-based ribavirin	12 weeks	I, B
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[b]	16 weeks	IIa, B

[a] For decompensated cirrhosis, please refer to the appropriate section.
[b] This is a 3-tablet coformulation. Please refer to the prescribing information.

Recommended Regimens

Elbasvir/Grazoprevir + Sofosbuvir

The C-ISLE study evaluated the daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus sofosbuvir, with or without ribavirin, for 8 weeks to 16 weeks for treatment-naive or -experienced, genotype 3-infected patients with compensated cirrhosis. One hundred patients were enrolled, including 53 with a history peginterferon/ribavirin failure. Treatment-experienced participants were randomized to 12 weeks of elbasvir/grazoprevir plus sofosbuvir, 12 weeks of elbasvir/grazoprevir plus sofosbuvir and weight-based ribavirin, or 16 weeks of elbasvir/grazoprevir plus sofosbuvir (Foster, 2016b). All 3 arms had 100% SVR on the per protocol analysis, with 17 patients in each arm. The efficacy was *high regardless of the presence of baseline RASs, including 3 patients with the Y93H substitution.*

Sofosbuvir/Velpatasvir/Voxilaprevir

The efficacy of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) in genotype 3 infection is supported by the phase 3 POLARIS trials, which investigated 8 weeks of sofosbuvir/velpatasvir/voxilaprevir in DAA-naive patients and 12 weeks in DAA-experienced patients. The 8-week regimen achieved noninferiority compared to a 12-week sofosbuvir/velpatasvir regimen in the POLARIS-3 study, which included 35 interferon-experienced patients with genotype 3 infection and cirrhosis (Jacobson, 2017). Thus, this regimen

is recommended in patients with genotype 3 infection and cirrhosis.

In the ASTRAL-3 study, which investigated 12 weeks of sofosbuvir/velpatasvir, the Y93H substitution was detected in 9% (25/274) of patients with an SVR12 rate of 84% (21/25) (Foster, 2015a). Patients with genotype 3 infection, prior non-DAA treatment failure, and cirrhosis are among the most difficult to treat. For this reason, ribavirin is recommended for all patients receiving sofosbuvir/velpatasvir, making this an alternative regimen. Due to the low number of patients with the Y93H mutation in the POLARIS-3 study, we recommend 12 weeks of sofosbuvir/velpatasvir/voxilaprevir to optimize SVR12.

Alternative Regimens

Sofosbuvir/Velpatasvir + Ribavirin

The phase 3 ASTRAL-3 study evaluated the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (without ribavirin) in 277 genotype 3-infected patients, including 71 with prior treatment experience and 80 with compensated cirrhosis (Foster, 2015a). Despite a high combined SVR12 rate of 95% (264/277), both prior treatment (90% SVR) and compensated cirrhosis (91% SVR) had a moderate negative impact on treatment response. Among those with both compensated cirrhosis and prior treatment, the SVR12 rate was 89% (33/37). The addition of ribavirin appeared to increase SVR12 rates in a phase 2 study that included treatment-experienced, genotype 3-infected patients treated for 12 weeks with sofosbuvir (400 mg) plus 25 mg or 100 mg of velpatasvir, with or without ribavirin (Pianko, 2015).

In the POLARIS-3 study noted previously, the SVR12 rate in the 32 patients with prior peginterferon/ribavirin treatment failure and cirrhosis was 91% (29/32). Although the 2 virologic failures did not have Y93H at baseline, both developed treatment-emergent Y93H mutations (Jacobson, 2017). Based on this finding and analogous to the similar ALLY-3 study, the addition of weight-based ribavirin (if not contraindicated) is recommended for all treatment-experienced, genotype 3-infected patients with compensated cirrhosis when using sofosbuvir/velpatasvir pending additional data. Due to the need for ribavirin, this is recommended as an alternative regimen.

Glecaprevir/Pibrentasvir

The SURVEYOR-II, part 3 trial evaluated the safety and efficacy of a 12-week or 16-week course of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose combination pills in treatment-naive or -experienced (standard or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon), genotype 3-infected patients without cirrhosis or with compensated cirrhosis. Among the 47 treatment-experienced participants with compensated cirrhosis who were treated for 16 weeks, the SVR rate was 96% (45/47). One of the virologic failures was a relapse and the other was viral breakthrough. The patient with viral breakthrough had low serum DAA levels at week 4 of the study, suggesting poor adherence. The patient with relapse did not have baseline NS3 or NS5A RASs but did have dual NS5A RASs emerge at the time of failure (Wyles, 2017a).

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DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis

Recommended regimen for: DAA-Experienced (Including NS5A Inhibitors), Genotype 3 Patients With or Without Compensated Cirrhosis[a]		
RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/ voxilaprevir (100 mg)	12 weeks	I, A
For patients with prior NS5A inhibitor failure and cirrhosis, weight-based ribavirin is recommended.	12 weeks	IIa, C
[a] For decompensated cirrhosis, please refer to the appropriate section.		

Recommended Regimen

Sofosbuvir/Velpatasvir/Voxilaprevir ± Ribavirin

The phase 3 POLARIS-1 and POLARIS-4 trials included patients with genotype 3 infection, without cirrhosis or with compensated cirrhosis, who had previously received a DAA regimen, with or without an NS5A inhibitor. The POLARIS-4 study included treatment-experienced patients who had previously received a DAA regimen but not an NS5A inhibitor. Participants were randomized to 12 weeks of the daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)/voxilaprevir (100 mg) (54 with genotype 3 infection) or 12 weeks of sofosbuvir/velpatasvir (52 with genotype 3 infection). SVR rates for the genotype 3-infected patients were 96% (52/54) and 85% (44/52), respectively. The 8 patients who experienced a relapse in the sofosbuvir/velpatasvir arm were primarily white males with compensated cirrhosis (7/8) and a high BMI (>25). Although none had baseline Y93H variants, all had emergence of Y93H variants at the time of relapse (Bourliere, 2017).

The POLARIS-1 study included patients who had previously received a regimen containing an NS5A inhibitor. Participants were randomized to 12 weeks of sofosbuvir/velpatasvir/voxilaprevir (78 with genotype 3 infection) versus placebo. The SVR12 rate was 95% (74/78) for the genotype 3-infected patients. All 4 patients who experienced a relapse had cirrhosis (Bourliere, 2017). These data support the use of sofosbuvir/velpatasvir/voxilaprevir for 12 weeks in all DAA-experienced patients. However, in NS5A inhibitor-experienced genotype 3-infected patients with cirrhosis, the relapse rate is higher and adding weight-based ribavirin is recommended to minimize relapse risk.

Last update: September 21, 2017

Treatment-Experienced Genotype 4

The following pages include guidance for management of treatment-experienced patients with genotype 4 infection.

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Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

Recommended and alternative regimens listed by evidence level and alphabetically for:

Peginterferon/Ribavirin-Experienced, Genotype 4 Patients Without Cirrhosis

RECOMMENDED	DURATION	RATING
Daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg)	12 weeks	I, A
Daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg)[a]	8 weeks	I, B
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) for patients who experienced virologic relapse after prior peginterferon/ribavirin therapy	12 weeks	IIa, B
Daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg)	12 weeks	IIa, B
ALTERNATIVE	**DURATION**	**RATING**
Daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin	12 weeks	I, A
Daily fixed-dose combination of elbasvir (50 mg)/grazoprevir (100 mg) plus weight-based ribavirin for patients with prior on-treatment virologic failure (failure to suppress or breakthrough) while on peginterferon/ribavirin	16 weeks	IIa, B

[a] *This is a 3-tablet coformulation. Please refer to the prescribing information.*

Recommended Regimens

Sofosbuvir/Velpatasvir

The double-blind, placebo-controlled ASTRAL-1 trial evaluated treatment-naive or -experienced patients with genotype 1, 2, 4, 5, or 6 infection treated with a daily fixed-dose combination of sofosbuvir (400 mg)/velpatasvir (100 mg) for 12 weeks (Feld, 2015). The study included 116 patients with genotype 4 infection. One hundred percent SVR12 was achieved, including 52 treatment-experienced patients (Feld, 2015).

Glecaprevir/Pibrentasvir

The phase 2, open-label, single arm SURVEYOR-II, part 4 study investigated the efficacy of 8 weeks of the daily fixed-dose combination of glecaprevir (300 mg)/pibrentasvir (120 mg) administered as three 100 mg/40 mg fixed-dose

combination pills in patients with genotype 2, 4, 5, or 6 infection without cirrhosis. Patients were treatment naive or experienced (interferon or peginterferon ± ribavirin, or sofosbuvir plus ribavirin ± peginterferon). Forty-six genotype 4-infected patients accounted for 23% of the study population; only 27 of these patients (13% of the study population) were treatment experienced. The SVR12 was 93%; 3 patients had nonvirologic outcomes, including missed follow-up and study discontinuation. There were no virologic failures but the number of treatment-experienced patients is small (Hassanein, 2016).

Elbasvir/Grazoprevir ± Ribavirin

A 2015 integrated analysis of all phase 2 and phase 3 elbasvir (50 mg)/grazoprevir (100 mg) studies to date demonstrated efficacy of this regimen for both treatment-naive (n=66) and -experienced (n=37) patients with genotype 4 infection (Asselah, 2015). The overall SVR12 rate among treatment-experienced, genotype 4-infected patients was 87% (32/37) with numerical response differences based on prior interferon treatment response (relapse vs on-treatment viral failure); elbasvir/grazoprevir duration (12 weeks vs 16 weeks); and/or ribavirin usage (inclusion or exclusion of ribavirin in the regimen). Numbers within any specific subgroup are too small to make definitive recommendations. However, trends emerged that were used to guide the current recommendations pending additional data. No treatment failures were seen in patients who relapsed after prior peginterferon/ribavirin therapy, regardless of elbasvir/grazoprevir treatment duration or ribavirin usage. In contrast, response rates were numerically lower in patients with prior on-treatment virologic failure in the non-ribavirin-containing arms (12 weeks, 78%; 16 weeks, 60%) compared to ribavirin-containing treatment (12 weeks with ribavirin, 91%; 16 weeks with ribavirin, 100%).

Given the lack of sufficient numbers to differentiate response between 12 weeks with ribavirin and 16 weeks with ribavirin, the use of 16 weeks of elbasvir/grazoprevir plus ribavirin in genotype 4-infected patients with prior on-treatment virologic failure represents the most conservative approach.

Ledipasvir/Sofosbuvir

In the open-label cohort, phase 2a SYNERGY trial, 21 patients with genotype 4 infection were treated with a 12-week course of the daily fixed-dose combination of ledipasvir (90 mg)/sofosbuvir (400 mg). Forty percent of participants were treatment experienced and 40% had advanced fibrosis. Twenty patients completed the 12-week therapy and all achieved SVR12; 1 patient withdrew from the study (Kohli, 2015). A pooled analysis of the 12-week ledipasvir/sofosbuvir regimen (including the SYNERGY trial) reported an SVR12 rate of 94% (32/34) in treatment-experienced patients with genotype 4 infection (Asselah, 2016).

Alternative Regimen

Paritaprevir/Ritonavir/Ombitasvir + Ribavirin

PEARL-I was an open-label, phase 2b study that included a cohort of 49 noncirrhotic, treatment-experienced patients (peginterferon/ribavirin) with genotype 4 infection who received 12 weeks of the daily fixed-dose combination of paritaprevir (150 mg)/ritonavir (100 mg)/ombitasvir (25 mg) plus weight-based ribavirin. Based on intention-to-treat analysis, SVR12 was achieved in 100% of these patients. The regimen was well tolerated with no serious adverse events reported (Hézode, 2015).

The phase 3, open-label, partly randomized AGATE-II trial enrolled genotype 4-infected, treatment-naive or -experienced (interferon-based therapy) patients, without cirrhosis or with compensated cirrhosis. The 100 noncirrhotic participants were treated with 12 weeks of paritaprevir/ritonavir/ombitasvir plus weight-based ribavirin. The SVR12 in this group of patients was 94% (94/100) (Esmat, 2015a).

These data support the use of paritaprevir/ritonavir/ombitasvir plus ribavirin for 12 weeks in treatment-experienced, genotype 4-infected patients. Due to the need for ribavirin resulting in a greater pill burden and adverse events profile, this regimen is an alternative recommendation.